INDONESIA

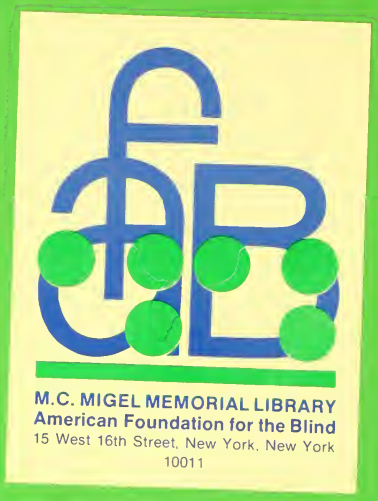
NUTRITIONAL BLINDNESS PREVENTION PROJECT

Characterization of Vitamin A Deficiency and Xerophthalmia and the Design of Effective Intervention Program

Final Report

September 1976 - July 1980

HELEN KELLER INTERNATIONAL INCORPORATED



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CONTENTS

PREFACE

The Nutritional Blindness Prevention Project--a large-scale investigation into the origins of vitamin A deficiency and nutritional blindness and what might be done to prevent them--was conducted from September 1976 through July 1980. The project was undertaken primarily at the initiative of the Indonesian Ministry of Health and Helen Keller International, and was administered by Indonesia's National Center for Health Research and Development and carried out under the direction of the Vitamin A Deficiency Steering Committee. Significant financial assistance was provided by the Office of Nutrition, Bureau of Technical Assistance, United States Agency for International Development. In large measure, however, the project's success reflects the contributions of many organizations and institutions and the devoted efforts of numerous individuals. To those whose names appear in Appendix B and to all others who helped bring this work to fruition, we are deeply grateful.

Vitamin A Deficiency Steering Committee
Jakarta, July 1980

I. INTRODUCTION

Nutritional blindness has long been recognized as a serious problem in Indonesia. In 1973 the Indonesian Government initiated a limited program to distribute capsules of high-potency vitamin A to children ages 1 to 4 as an emergency measure in 20 Kabupatens* or districts in Java. In the same year, the Government collaborated with the American Foundation for Overseas Blind--subsequently renamed Helen Keller International (HKI)--to evaluate the efficacy, cost, and efficiency of this pilot program. The results indicated that although regular administration of vitamin A capsules reduced the occurrence of mild forms of xerophthalmia, the incidence of the disease among untreated children indicated a problem of enormous proportions and raised questions about etiology which needed answers before an effective program could be developed to control the disease.[1]

In June 1975, the Ministry of Health set up a Steering Committee to explore, in conjunction with representatives of HKI, the possibility of conducting a large research project to identify the major obstacles to developing a national program for the prevention of nutritional blindness.

These obstacles included inadequate information on the following:

- The underlying cause of the conjunctival and corneal changes traditionally ascribed to xerophthalmia and the relative contributions of vitamin A deficiency, protein deficiency, diarrhea, measles, local ocular infections, and other systemic diseases in their etiology.

- The epidemiologic determinants of vitamin A deficiency, xerophthalmia, and nutritional blindness--such as age, sex, seasonality, clustering, feeding practices, socioeconomic status, general nutritional status, intercurrent infections, and demographic characteristics--that might identify variables amenable to intervention.

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*Kabupatens are the major administrative districts within a province.

- The natural history of night blindness, Bitot's spots, and conjunctival xerosis; the relationship of these symptoms to corneal pathology; the validity of the concept of sequential stages of xerophthalmia; and the potential value of using these milder signs of the disease to identify children who are at increased risk for nutritional blindness.
- The most practical and effective form of vitamin A therapy for xerophthalmia.
- The mechanisms by which vitamin A intake among young children might be increased.
- The potential value of periodically administering a massive dose of vitamin A to prevent nutritional blindness.
- The prevalence* and magnitude of xerophthalmia in the heavily populated areas of Indonesia.
- The incidence** of xerophthalmia.
- The relationship between the prevalence of Bitot's spots in a community and the risk of nutritional blindness among its residents.

To obtain this information, the four basic studies described in Section III were designed and carried out.

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*The term prevalence means the rate at which a condition, regardless of its duration, is present in a population.

**The term incidence means the rate at which new cases arise over a given period (e.g., one per thousand per year) in a population that was previously free of the disease.

II. CONCLUSIONS AND RECOMMENDATIONS

1. Xerophthalmia is a serious problem in Indonesia. More than 60,000 children develop gross corneal involvement every year; at least one-third of them are left permanently blind or visually impaired in both eyes. Taking all criteria as a whole, the disease seems especially prevalent in the following 15 provinces (listed from highest to lowest):

Aceh	Bali
Lombok	South Sulawesi
Bengkulu	Ambon
West Sumatra	South Kalimantan
South Sumatra	West Kalimantan
West Java	North Sumatra
Central Java	Southeast Sulawesi
Central Kalimantan	

Recommendation. To prevent this needless loss of sight in Indonesian children, the vitamin A deficiency intervention program should be expanded and intensified as rapidly as possible.

2. Mortality, especially among untreated cases is extremely high, although a large proportion of these deaths were undoubtedly related to systemic illness and generalized malnutrition that commonly accompany blinding forms of the disease.

3. Interference with vitamin A metabolism was the final common pathway of all forms of nutritional blindness encountered, and vitamin A deficiency was the root cause of this problem.

Recommendation. Efforts should be made to increase the intake of vitamin A in the at-risk population.

4. Although many factors may contribute to vitamin A deficiency, inadequate consumption of foods rich in vitamin and provitamin A was strongly associated with clinical disease.

Recommendation. Programs to increase the consumption of foods rich in vitamin and provitamin A should be initiated.

5. Xerophthalmic children eat green leafy vegetables (glv), a good source of beta carotene (provitamin A), far less frequently than do normal children, especially after the second year of life. Yet these

foods are apparently inexpensive and widely available in Indonesia: a majority of xerophthalmic children ate some glv, and 99 percent of all families ate them regularly (at least once a week) and 80 percent of all families ate them at least once a day.

Recommendation. Nutritional education programs should be aimed at increasing the frequency (and amount) of glv consumed by preschool children. In a few areas such as Aceh, availability of glv may be a limiting factor.

6. The commonest reason cited for children not consuming glv was simply that they did not like them. But a substantial proportion under age 2 were denied glv because their mothers either considered these vegetables to be inappropriate or did not know how to prepare them for children this young.

Recommendation. Several "messages" should be delivered to increase consumption of glv by young children.

7. Although only a small proportion of xerophthalmia cases occur during the first two years of life, these cases are often the most severe. Unfortunately, few children below age 2 eat glv. More important dietary determinants of xerophthalmia in this age group are frequency of consumption of papaya and breast feeding practices.

Recommendation. Nutritional education programs should encourage breast feeding and consumption of mango and papaya among this age group in addition to stressing consumption of glv.

8. Consumption of edible fat, essential for efficient absorption and utilization of ingested vitamin and provitamin A, is lower among xerophthalmic children than nonxerophthalmic children.

Recommendation. The intake of lipids (fat) should be encouraged and lipids should be eaten with glv, fruits, and other sources of provitamin A.

9. A majority of xerophthalmic children and an even larger proportion of their families consume three potentially fortifiable items: monosodium glutamate (vetsin), refined sugar, and wheat. A larger proportion consume more MSG than either of the other items.

Recommendation. The feasibility of fortifying MSG with vitamin A should be explored as an additional means of increasing vitamin A intake.

Unfortunately, a majority of children in two small but high-risk areas, Aceh and Lombok, do not consume MSG; thus fortification would be less effective in these areas.

10. Oral administration of 200,000 IU of oil-miscible vitamin A every four to six months will prevent xerophthalmia in the majority of children who receive these doses.

Recommendation. To be effective, programs must insure that children at highest risk actually receive the vitamin. Methods should be sought for distributing capsules efficiently to children who live in particularly high-risk areas, at least until other measures alleviate the problem. The capsules of 200,000 IU vitamin A can be administered at relatively low cost and great benefit to all children who are severely ill, are malnourished (especially those with edema), or have active measles because they are at particularly high risk of corneal destruction and blindness. Administration of 200,000 to 400,000 IU to every mother and 50,000 IU to every infant immediately after birth is likely to prevent much of the disease during the first year or more of life. Lactating mothers should receive additional doses of 200,000 IU every two to four months. Capsules should be available at all clinics, and health personnel must be trained to use them.

11. Oral administration of 200,000 IU of oil-miscible vitamin A upon diagnosis, the following day, and again after two weeks provides adequate systemic vitamin A therapy for active xerophthalmia. Oil-miscible injections are less effective and are more likely to result in early relapse. Although an injection of a water-miscible preparation is as clinically effective as an oral dose, it offers no obvious advantages and many obvious disadvantages: e.g., the preparation is more expensive and less stable, and injections require needles, syringes, and trained medical personnel. In contrast, oral dosing is simple, inexpensive, and safe (except for occasional cases of transient asymptomatic papilledema, there was little evidence of toxicity).

Recommendation. Capsules should be available at all points in the health delivery system for the treatment of xerophthalmia. Injection of oil-miscible preparations should be strongly discouraged.

12. Severely malnourished xerophthalmic children did not absorb and utilize vitamin A well.

Recommendation. Severe protein-energy malnutrition should be corrected, and doses of vitamin A should be repeated until this occurs (e.g., by administering a fourth oral dose after four weeks).

13. Corneal involvement was frequently accompanied by severe protein-energy malnutrition, which exacerbated existing vitamin A deficiency.

Recommendation. Mothers of severely xerophthalmic children should be taught how to feed and care for their children properly (and in a manner that is appropriate to their often limited resources).

14. A high proportion of blinding xerophthalmia was apparently precipitated by measles.

Recommendation. An effective measles vaccination program would probably have an appreciable impact on the problem.

15. Vitamin A deficiency and xerophthalmia occur in clusters.

Recommendation. It might be more efficient to administer vitamin A to all children residing in the immediate vicinity of a known case of clinical disease rather than treat only the one case.

16. A history of night blindness can be a simple, sensitive, and specific means of identifying individuals who need vitamin A therapy.

Recommendation. Innovative screening programs, such as having school children identify younger siblings and neighbors who are night blind, should be formulated and tested under a variety of conditions and in a variety of communities. Care must be taken so that inquiries will be culturally appropriate.

17. Among preschool children, Bitot's spots are a specific sign of active vitamin A deficiency. Correlations between the prevalence of Bitot's spots, active corneal disease, and xerophthalmic scars suggest that one WHO criterion for a significant public health problem--a prevalence of Bitot's spots of 2 percent--is far too high for Indonesia.

Recommendation. The more realistic level of 0.5 percent should be adopted for Indonesia.

18. Severe corneal xerophthalmia can occur in the absence of obvious conjunctival changes.

Recommendation. In the presence of classical corneal involvement, lack of Bitot's spots or conjunctival xerosis should not be interpreted as an absence of vitamin A deficiency or xerophthalmia.

19. Although a number of additional clinical, socioeconomic, and demographic factors were associated with xerophthalmia, they either were not present in a significant proportion of cases or were too common among normals to serve as useful avenues for intervention.

20. Building on the knowledge and facts gained from this research, the Government of Indonesia is now in a position to expand and intensify efforts to intervene in the problem, and actions have already been initiated in several program areas.

Recommendation. We suggest that the Government extend or modify existing programs or undertake additional ones, if indicated, in order to develop a comprehensive approach to the problem. Such an approach should include efforts to

- Fortify a suitable food consumed by xerophthalmic children,
- Distribute high-potency capsules of vitamin A to children at risk through the most cost-effective systems,
- Refine the messages delivered by nutrition and health educators according to the research findings, and speed up their delivery, using appropriate and effective methods of communication to bring about behavioral change, and
- Give health personnel the advantage of new knowledge about and control of xerophthalmia and make a systematic effort to integrate this knowledge into training programs for these personnel at all levels.

In addition, systems for monitoring and evaluating the impact and effectiveness of intervention activities should be established as soon as possible.

III. RESEARCH DESIGN AND METHODS

Project headquarters were located at the Cicendo Eye Hospital in Bandung. Except for detailed clinical charts compiled in Studies II and III, all forms were precoded for direct transfer to 80-column IBM cards and were reviewed and edited by the project's statistics section for punching. The statistics section also compiled simple, hand-tabulated analyses on a sample of incoming data to monitor the teams' performance and progress and identify critical and unexpected results that required further investigation.

In large part, the studies were interrelated: i.e., the results of one were used to confirm or expand those of another. For example, children with active cases of corneal xerophthalmia identified in Study I were hospitalized and included in Study II, and patients from studies II and III were used to train and standardize the teams that carried out Study IV. All study teams were trained for at least two to three months, then standardized and field tested.

Statistical tests included the normal deviate (z) corrected for continuity, the chi square (x^2) test with the Yate's correction, Fisher's exact test, the Student's t test for paired and unpaired samples, tests for linear trend, and correlation and regression analyses.[2, 3, 4]

Study I

Study I was a longitudinal, prospective study of roughly 5,000 preschool-age rural children, who were reexamined every three or four months for almost two years. The study was carried out in six villages in Purwakarta, a Kabupaten in West Java, which were chosen after a review of local clinical records and exploratory minisurveys demonstrated that these villages had a high incidence of xerophthalmia.[5]

As a preliminary step, the six villages were mapped and all houses were numbered. Next, members of the field team visited all houses, enrolled all families that had children under age 6, and affixed a study number to each family's house. Vital statistics and socioeconomic data were collected on the family and each individual member. The name, age, sex, and study number of each family member was recorded in a census book and on a registration card that remained in the home. Team supervisors then revisited 10 to 20 percent of all houses to check the accuracy of the information.

Clinical Rounds

Seven regular clinical rounds were carried out between March 1977 and December 1978. Midway through the seventh round, a special validation study was instituted in which all children exhibiting symptoms of xerophthalmia--night blindness, Bitot's spots, or conjunctival xerosis--were randomly assigned to receive one of two capsules that were identical in appearance: one contained 200,000 international units (IU) of retinyl palmitate (Vitamin A) in oil and 40 IU of vitamin E; the other contained 700 IU of retinyl palmitate in oil and no vitamin E. A supervisor assigned the children to one of two groups and administered the capsules. The team physicians were deliberately not told which capsule each child received. Three weeks after taking the first capsule, the children were reexamined in double masked fashion and given a high-potency capsule. These post-treatment reexaminations constituted a special eighth "validation" round to document the disease's responsiveness to vitamin A.

All examinations were carried out by one team composed of an ophthalmologist, a pediatrician, two supervisory nurses, and eight enumerators. The enumerators went from house to house, updating basic demographic data and identifying all study children with the help of the census book and the registration card retained by the family. All available children were brought to a central point, where the ophthalmologist examined their eyes with a hand light, the pediatrician gave them a general physical examination, and a nurse measured their height and weight with a calibrated "dacin" or bar balance and a "microtoise".

The nutritionist collected dietary histories in masked fashion on all children with active xerophthalmia, their matched controls (the next

child encountered in the neighborhood, RT,* who was the same age and sex), and a preselected subsample of the study population as a whole. The children with active cases were then divided into the following groups, according to their symptoms (see also, Table 4):

XN	Night blindness (secondary sign)
X1A	Conjunctival xerosis
B	Bitot's spot with conjunctival xerosis
X2	Corneal xerosis
X3A	Corneal ulceration with xerosis
B	Keratomalacia
XF	Xerophthalmic fundus (secondary sign)
XS	Corneal scars secondary to xerophthalmia

During the first clinical round, fingertip blood samples were obtained from all children with active xerophthalmia and their matched controls and from half the children in the subsample, which represented 10 percent of all children in the study. (During the second round, the subsample represented only 5 percent of all children in the study.) All children with corneal involvement (or, after the second clinical round, 180 degrees or more of conjunctival xerosis) were immediately offered hospitalization and treatment. Parents of children who did not have severe xerophthalmia but were severely malnourished or had a life-threatening illness were advised to take their children to the local Puskesmas** or hospital, and transportation was provided when necessary. Children with a moderate cough were given decongestants; those with diarrhea received oralyte.

The subsample was preselected at project headquarters in Bandung. For the first round, all study families were serially arranged, beginning with family 1, RT 1, village Cilegong. After a random start between 1 and 10, every tenth family was systematically included. Blood samples were obtained from all preschool-age children in every other family in the subsample. In each subsequent round, the original start was advanced one number, the process was repeated, and every twentieth family was

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*An RT or neighborhood often consists of 10 to 35 houses.

**A Puskesmas is a local, government-run clinic.

included. Interviews were conducted in either the Sundanese or Indonesian language since the enumerators were fluent in both.

Special procedures for recording xerophthalmia were established in all four rural health clinics in the study area so that the final results could be corrected for participants who received vitamin A therapy from any one of the clinics.

Eligible children who were either born or moved into study households were added to the study. Families that lacked preschoolers during the census-survey were never included in the study.

Diagnostic Definitions

Conjunctival dryness. One or more patches of granular unwettability, aptly described as looking "like sandbanks at receding tide." Many examples of this type of lesion were observed among hospitalized patients, and the ophthalmologists in all four studies were able to recognize them easily.

Conjunctival foam or bubbles. This symptom is more obvious than conjunctival dryness. When present, the foam was removed with a cotton-tipped applicator so that the xerosis, if any, could be observed.

Conjunctival pigmentation and thickening. Because these symptoms were difficult to standardize, defining them was left to the ophthalmologist.

Corneal involvement. Corneal involvement, like conjunctival lesions, was often encountered among clinic and hospital patients, and the reproducibility of diagnoses was high. All cases were referred to study II, where they were carefully examined and classified.

Night blindness. To obtain a history of night blindness, a parent or guardian was asked whether the child suffered from "buta ayam" or "kotokeun" (chicken eyes). In rare instances where these terms were not recognized, the respondent was asked whether the child was unable to locate food or toys after dusk. The diagnosis was accepted as positive only when the respondent was certain of its presence and the child's age at onset and clearly indicated that the child's behavior differed from that of his peers. The diagnosis was also regarded as positive if the respondent said the child was night blind only after a photic stress such as flying a kite on a sunny day.

Early in the first clinical round, objective assessment of scotopic vision among children with a history of night blindness was added to the examination. In most instances, the ophthalmologist or a carefully trained field worker returned after dusk and compared the child's ability to locate a piece of candy or a toy with that of normal peers (as determined by their histories). On subsequent rounds, the child was placed in a darkened room, allowed to adapt for 15 minutes, and then asked to locate his mother, who stood six to ten feet away.

Analyses

Cooperation remained high in all villages throughout the study, except in the conservative village of Citeko, where the parents of 25 to 50 percent of the study children refused to have them examined. For this reason, the results for Citeko were analyzed both together with and separately from the results obtained from other villages to determine whether there were any peculiarities or biases in the data.

To make the field work more efficient and shorten the intervals between examinations, the study population was reduced at the end of the first clinical round from approximately 5,000 to about 4,000 preschool children by excluding several contiguous RTs in which the children did not exhibit Bitot's spots. All analyses of incidence and the relationship between incidence and prevalence are limited to the remaining RTs. Four RTs that were deleted by mistake during the second clinical round and reinstated again in the third are also included in the analyses.

Blood specimens

Between 400 and 600 ul of blood were collected in unheparinized capillary tubes at the central point, sealed with molten wax, placed in a sealed test tube, and stored in a covered chest filled with ice. The samples were spun the same evening at field headquarters, and the clear serum was separated by snapping the capillary tubes above the level of the packed cells. The tubes were then resealed, packed in ice-filled containers, and shipped each weekend to the biochemistry laboratories at the Nutrition Research Institute in Bogor. Serum levels of vitamin A were usually analyzed within one week (never more than two weeks) after the samples were drawn, using the micromethod of Neeld and Pearson.[6] One capillary tube of blood was analyzed spectrophotometrically for

hemogoblin with Drabkin reagent at field headquarters on the day the blood was obtained.

Market Patterns

One small, local store (or warung) from each RK* was visited during each clinical round to determine the availability and cost of an itemized list of foods.

Studies II and III

Studies II and III were prospective, detailed clinical, biochemical, bacteriologic and histopathologic studies of children with corneal (Study II) and noncorneal (Study III) xerophthalmia. These children were enrolled in a variety of therapeutic and diagnostic trials. A sample of corneal cases was selected for epidemiologic field studies that yielded matched controls for comparison.

Study III was originally designed as a long-term field study to determine the effectiveness of administering massive oral doses of vitamin A periodically to xerophthalmia. The results of the minisurveys conducted in Study I indicated that the prevalence of corneal scars was insufficient to support such an approach. Therefore, cases of corneal and noncorneal disease were included in Studies II and III with long-term follow-up as an alternative, albeit less direct approach.

Source of Patients

All patients, regardless of age, who came to the Cicendo Eye Hospital between June 1977 and June 1978 with signs or symptoms of xerophthalmia were automatically enrolled in the study. Additional patients with corneal involvement were recruited from the Cikampek Clinic and from Study I.

Matched controls of corneal cases (matched by age, sex, and neighborhood), identified in the course of the field investigations, were encouraged to come to Cicendo and undergo similar examination and treatment. Sixty percent of them actually did so.

Clinical Evaluation

All children received complete ophthalmologic and pediatric evaluations

*An RK is a major subdivision of a village. A village often contains three to ten RKs, and an RK often contains three to ten RTs.

(including anthropometric measurements). The ocular examinations were carried out in the following order: (1) examination with a hand light and slit lamp, with and without sterile fluorescein, (2) corneal swabbing and scraping for bacteria and fungi if ulcers were present, (3) Lissamine Green staining,[7] (4) Schirmer test under topical anesthesia, (5) application of dilating drops, (6) adaptation to the dark for 30 minutes, (7) examination for night blindness, and (8) indirect ophthalmoscopy. All lesions were carefully drawn, and all eyes were photographed.

Night blindness was assessed by evaluating the child's ability to locate a parent or guardian who stood eight feet away in a room darkened to the degree where a normal observer could read headlines but not ordinary newsprint after adapting for ten minutes.

Dietary and Socioeconomic Data

A nutritionist obtained dietary histories, and a specially trained enumerator collected socioeconomic data from all families. This information was recorded on forms similar to those used in Study I.

Follow-up Examinations

In general, children with corneal involvement discovered in Study II were hospitalized; those without corneal involvement (Study III and controls) were not. Hospitalized children were examined daily. All nonhospitalized children were examined according to the following schedules (day 0 = the initial examination):

Study II	Study III
Each day for one week	Day 1
Once a week for four weeks	Day 3
Monthly thereafter	Week 1
	Week 2
	Monthly thereafter

Although every effort was made to follow all patients at regular intervals, parents unfortunately saw little reason to return once their children began to improve. When they failed to appear for two successive visits, a letter was sent to the home urging them to return. In the case of severely ill corneal cases, a staff member visited the home if the parents failed to respond to the letter. When the study was completed, the staff visited the home of each child who was not seen during the final two months. If present, the child was taken to the hospital for

an examination. If the child was not present, information about his or her whereabouts was sought from relatives and neighbors. If the family had moved to a new address in West Java and the address was known, the home was visited. If the child had died, the date and apparent cause of death were recorded.

Biochemical Studies

Three ml of veinous blood were collected from each child, transferred to capillary tubes and spun in a centrifuge, and the clear supernatant was stored at -20°C. Vitamin A determinations were usually carried out within one week after the samples were collected, never after more than two weeks. Determinations of holo-retinol binding protein (RBP) were usually carried out within two months, never more than eight months after collection. Samples were analyzed at laboratories in Bogor in masked fashion for content of vitamin A,[5] holo-RBP,[8] prealbumin, total RBP, and transferrin.[9]

Blood samples were collected from all patients and controls during the initial examination (at "0" hours), and according to the following schedule thereafter:

Study II (patients and controls)	Study III
1 hour	1 hour
4 hours	
1 day	1 day
2 days (initially only)	
3 days	3 days
1 week	1 week
2 weeks	
3 weeks	
4 weeks	
Monthly	Monthly

Because of equipment failure, vitamin A determinations were not available between July 16, 1977, and January 14, 1978 (electrical malfunction of the spectrophotometer), and holo-RBP determinations were not available after May 15, 1978 (electrical malfuntion of the chromoscan).

Microbial Studies

Material obtained from swabs and scrapings were smeared for immediate evaluation and directly plated or innoculated onto the following media for bacterial and fungal culture: blood agar, chocolate agar, Saubouraud's (x2), and bouillon. All analyses were carried out in masked fashion at the Bio-Farma laboratories in Bandung. Stool

specimens, when available, were examined at the Department of Public Health, UNPAD, for ova and parasites.

Histopathologic Studies

In selected cases, small conjunctival biopsies of 1x2 mm were obtained from either the temporal or nasal quadrant and from the inferonasal quadrant under topical ophthaine or subconjunctival xylocaine anesthesia when the examination was completed. Topical antibiotic ointment was applied to the biopsied areas; the eye was then patched and examined daily until healing was complete (usually within two to four days). In some instances, the conjunctiva of the patient's other eye was biopsied at a preselected interval after treatment to study the resolution of the lesion. Light, transmission, and scanning electron microscopy was carried out in the eye pathology laboratories at the medical schools of Johns Hopkins and Harvard universities.

Treatment and Diagnostic/Therapeutic Trials

Study III. Unless severely ill, patients with isolated night blindness or conjunctival lesions were generally treated as outpatients. At the beginning, patients who had been assigned an "odd" number received a coded capsule containing 200,000 IU of vitamin A and 40 IU of vitamin E; those assigned an "even" number received a capsule containing 700 IU of vitamin A. Children age 8 or older were the exception to this rule because we suspected that a significant proportion of these rare cases had unresponsive Bitot's spots. Rather than risk losing these children, undiagnosed, during prolonged follow-up, all of them received the high-potency capsule.

All patients received a high-potency capsule after three months, or sooner if their condition had deteriorated. Because the condition of a sizable proportion (11 of 18 eyes) of the children who received low doses of vitamin A did deteriorate clinically, the use of the capsules containing only 700 IU was discontinued early in the study. Thereafter, all patients received 200,000 IU of vitamin A during their initial examination.

Study II. All patients with corneal involvement were encouraged to enter the special study ward established at Cicendo for complete and often urgently needed systemic therapy, which included rehydration,

feeding, antibiotics, treatment for tuberculosis, and so forth. They had chest X-rays, stool examinations for ova and parasites, skin tests for tuberculosis, and additional tests required to treat their systemic illnesses.

All hospitalized patients received a high-protein diet (at least 15 gms per day, if possible) and some form of systemic vitamin A therapy. When necessary, they were fed through a nasogastric tube. Those with corneal perforation received 50,000 IU of penicillin G/kg (or cloxacillin equivalent) each day for at least seven days.

The nutritionist recorded the dietary intake of all ward residents, and every effort was made to keep the children on the ward for at least two weeks. Some parents, however, insisted on taking their children home sooner; others refused to hospitalize their children at all.

Three forms of systemic vitamin A therapy were employed:

1. Initially, children assigned odd numbers received oral doses of 200,000 IU of oil-miscible vitamin A, and children assigned even numbers received intramuscular injections of 100,000 IU of water-miscible vitamin A.

2. Because many severely malnourished children responded poorly to a single dose or relapsed soon after receiving it, subsequent patients were placed on one of the two regimens described above and were given an additional 200,000 IU of oil-miscible vitamin A orally the following day.

3. Because the supply of water-miscible injectable vitamin A eventually ran out, the last 50 patients were placed on the double-dose oral regimen or received 200,000 IU of oil-miscible vitamin A intramuscularly in two doses when admitted to the study. Children who seemed to respond poorly to either regimen received one or more additional doses two or three weeks later. Those who were gravely ill were transferred to the pediatric ward of the general hospital (Hasan Sadikin) but remained in the study.

Two types of topical therapy were used in cases of corneal perforation:

1. To determine the possible role of bacterial infections in the genesis of corneal lesions and the need for antibiotic therapy, 27 consecutive hospitalized patients with corneal ulceration received topical antibiotic ointment (mycetracin plus garamycin) five times a

day in the right eye, none in the left. (One child whose lesions were obviously infected was excluded from this trial and automatically received antibiotic treatment.) The trial was discontinued if a single untreated eye fared substantially worse than the perfectly matched treated eye (this topic is discussed in detail later). All subsequent patients with corneal ulceration received both topical and systemic antibiotics.

2. Fifty consecutive patients received three topical applications of 0.25 cc of 0.1 percent retinoic acid in sterile arachis oil in one eye for seven consecutive days. The other eye received sterile arachis oil. In cases where both eyes were affected to an equal degree, the drug was placed in the right eye of half the patients and in the left eye of the other half. When corneal involvement was unequal, the drug was placed in the more severely affected eye. Patients with "open" eyes (complete corneal perforation) were excluded from this trial.

Epidemiologic Investigations (Study II)

Using forms and procedures similar to those employed in Study I, the Study II team visited the neighborhoods of a subsample of corneal cases. Beginning at the house containing the active corneal case, approximately 15 neighboring houses were visited, and 25 preschool children were examined and their socioeconomic status evaluated. Blood samples and dietary histories were obtained for all children who were the same age in years as the index cases, all children discovered to have active xerophthalmia, and all children in five randomly selected families.

Children who were the same age and sex as the index cases (Study II corneal) were designated as matched controls and were encouraged to return to Cicendo for examination.

Similar data had already been collected on the index cases.

Study IV

Study IV was a national survey on the prevalence of xerophthalmia/nutritional blindness conducted in 23 of the 27 provinces of Indonesia. Our goal was to obtain a representative sample of preschool-age children from each major population area that would be large enough to ensure the detection of active conjunctival lesions and old, healed corneal disease at the minimum prevalence deemed by WHO to indicate a significant public

health problem[10] and to identify major differences that might exist between areas where the prevalence was high or low. These populous areas were divided into 6 zones that best represented the country's cultural and administrative differences. Rather than choose a sample with a probability proportional to size for the country as a whole, samples of equal size were chosen in each zone to provide the minimum sample necessary to obtain statistically valid estimates of corneal disease within each. Overall country rates were calculated by applying weighting factors, proportional to population size, to the zonal rates.

The number of children per zone that seemed to satisfy the statistical requirements and simultaneously fit the practical constraints of time, money, and personnel was 7,500.[11]

Since it was impossible, from a practical standpoint, to examine all areas of Indonesia, the country was divided into six zones covering the overwhelming majority of the population (96 percent).[12] Five zones were represented in their entirety: East Java, Central Java (including Jogyakarta), West Java (including Jakarta), Sumatra, and Sulawesi. The remaining zone was composed of a representative sample, of more limited size, on the islands of Kalimantan, Lombok, Bali, and Ambon.

Basic Sampling Structure

A stratified, multistage, cluster sampling technique was carried out as follows:

1. The country was stratified into the 6 zones.

2. Each stratum was restratified into urban and rural areas.

3. Since a team could examine roughly 120 rural children and 250 urban children per day, each rural cluster was designed to yield 120 children, and each urban cluster, given the fewer sites available, was designed to yield 500. Sufficient clusters were then assigned to each zone to yield the desired number of children.

4. To increase efficiency, urban samples were selected to represent only the slums, not the urban areas as a whole, because experience indicated that the vast majority of urban cases arose in these areas. Therefore, the results from urban areas indicate areas of obvious risk, not true prevalence. When necessary, urban areas can be approximated by adjusting the observed prevalence for the proportion of urban dwellers who live in the slums.

Selection of Sample Sites

Use of Intercensal Survey as sampling frame. A review of the sampling procedures used in a well-designed population survey carried out by the Central Bureau of Statistics (CBS) in 1976[13] indicated that, with modification, the CBS sample would provide an excellent basis for our sampling frame. In addition, the CBS could also supply us with maps defining each cluster and with lists of its inhabitants, which would be useful for further defining the cluster. Furthermore, the multiple variables assessed in each CBS cluster could be correlated with our own.

Selection of sample clusters from sampling frame. The clusters of the SUPAS II subsample of the Intercensal Population Survey served as the sampling frame for the project survey. First, the sampling frame was separated into zones, provinces and islands. Each zone was then stratified into rural (nonmunicipality) and urban (municipality).

Rural sample sites within each zone were already chosen, for SUPAS II, with a probability proportional to size (PPS). Roughly 36 clusters were required for each rural zone. The total number of clusters in each zone in the Supas II frame was divided by 36, yielding the required sampling ratio. After a random-number start between sites 1 and the sampling interval (e.g., 3, 4, and so forth), every site falling at the required interval was chosen. This systematic sampling technique preserved the randomness and PPS of the original SUPAS II selection. The teams were required to visit all families within the cluster. If these visits yielded less than the required 120 children, the cluster's boundaries were enlarged to include adjacent areas of similar socioeconomic composition to make up the difference.

The urban sample was composed of the slum areas of major municipalities. The slums were identified by local census and health authorities.

For zone 6, composed of a variety of islands, a larger number of rural sites were included to provide a sample size sufficient for estimating rates in each, although these rates were less precise than zonal rates. The number of sites in zone 6 were as follows--Bali: 11 rural, 1 urban; Lombok: 20 rural, 0 urban; Kalimantan: 19 rural, 4 urban (one per province); and Ambon: 9 rural, 0 urban. Sites in all but Ambon were selected in the systematic manner just described. (A

representative rural sampling of Ambon was not included in the Intercensal Survey.)

In Ambon, sampling was carried out in three stages. First, nine RKs were chosen from a list of all RKs ordered by population at a systematic sampling ratio of 20,000 persons per site. Second, one RT was randomly selected from among all RTs in each selected RK. Third, a census block was chosen at random within each RT.

When we discovered that four selected sites in West Java and two in East Java were already a part of the capsule distribution scheme, we deleted them, since they were no longer representative of the area, and substituted adjacent villages in the SUPAS II frame.

Only five preselected sites eventually had to be deleted from the survey because they were inaccessible--one each from East Java, Central Sulawesi, North Sulawesi, South Sulawesi, and Aceh.

Modifications of Original Protocol

The number of sites just described, and thus the number of children in the survey, was less than projected in the original protocol.[11] This reduction was necessary when more realistic estimates of travel time and accessibility during the survey (which was conducted during the wet season: October through April) indicated that it would be impossible to cover the original sample with the available time, money, and personnel. The survey was scheduled during the wet season to avoid both the election and Ramadan and Lebaran, during which dietary habits are likely to be altered.* (The survey began in Bali, a Hindu area, to minimize the effect of Lebaran.)

Preliminary Visits to Sample Areas

During May and June 1977, project staff wrote to and visited appropriate Provincial Government authorities to obtain official permits and local support. During these visits, local census officials were contacted to locate sample villages and obtain detailed sample cluster maps. Provincial and local counterparts appointed by the Health Inspector

*During the Moslem holy month of Ramadan, the population eats breakfast before sunrise, eats dinner after sunset, and fasts between the two meals. Ramadan concludes with Lebaran, a period of feast and celebration.

were contacted to help detail survey procedures and determine time schedules, travel routes, and local transportation requirements as well as find lodgings and financial channels for use by the survey teams and the best means of sending completed forms back to Bandung.

Composition and Training of Survey Teams

Three survey teams were recruited in June 1977, each composed of one ophthalmologist, one nutritionist, one nurse, and five enumerators. The teams received three weeks of intensive training, including standardization, before visiting any sample sites. The three ophthalmologists spent one week at Cicendo Eye Hospital in Bandung to become better acquainted with the signs of xerophthalmia and the survey forms.

All team members attended lectures and participated in discussions on survey procedures, interviewing techniques, anthropometric measurements, and use of the survey forms during one week of classes held at project headquarters. This was followed by field training in rural villages of West Java and Bali, during which the teams received continuous supervision and were standardized.

Survey Forms

Simple self-coding forms that had been pretested in the field were used to record basic socioeconomic data on every family and the health, dietary history, height, weight, and results of the eye examination on each child.

Form 40X: Record of general information on each sample village (filled out by the nutritionist).

Form 40: Census list of families with children under age 6 (filled out by an enumerator).

Form 40NX: Record of basic socioeconomic data on the family as well as its food consumption pattern (filled out by an enumerator).

Form 41NX: A record of each child's medical background, height, and weight (filled out by an enumerator) and the results of the eye examination (filled out by the ophthalmologist).

Form 42NX: Dietary data on each case of xerophthalmia, its normal control matched according to age and sex, and a randomly selected subsample representing 20 percent of all study children (filled out by the nutritionist).

Forms 40NX, 41NX, and 42NX contained a strip listing all the results that could be torn off and mailed separately from the completed form. This enabled immediate hand tabulations and reduced the risk of losing all the data during shipment to Bandung. A detailed survey manual was provided to every team member.

Local Activities

Prior to the team's visit, the local counterpart contacted and informed each village authority about the survey operation and asked him to ensure that families in the sample site would remain at home on the day of the survey. Upon arriving at a sample site, the clinical team (the ophthalmologist, the nutritionist, the nurse, and one enumerator) established one or more central examination points while the other four enumerators, accompanied by local guides, visited every house, compiled socioeconomic data on form 40NX, and collected the children under age 6 for their examinations. Because of cultural taboos, children less than 2 months old were generally not examined.

The ophthalmologist examined the anterior segment of each child's eyes with a hand light, noted obvious abnormalities, and estimated the child's potential visual acuity as better or worse than 20/200. He paid special attention to lesions that were potentially related to active xerophthalmia (conjunctival xerosis, Bitot's spots, corneal xerosis, and keratomalacia) and its healed sequelae. Based on historical data provided by an older family member, he assigned one of the following etiologies to all healed corneal abnormalities:

Congenital:	Abnormality was noted at or shortly after birth in an otherwise white and quiet eye.
Trauma:	A clear-cut history of injury at the time of onset of corneal damage.
Infection:	Gross purulence, especially in children who were less than 2 months old at onset.
Xerophthalmia:	None of the above, in children who were at least 2 months old and usually ill or malnourished at the time of onset.

The enumerator at the central examination point measured the height and weight of every study child. Standing height was determined

with a microtoise measuring tape; the length of babies was measured in a specially constructed sliding frame. Weight was measured with a "Dacin" bar scale.

The nurse assisted the ophthalmologist in conducting eye examinations and selecting random children and normal matched controls.

The nutritionist completed the diet interview for all random children, abnormals, and matched controls in masked fashion. The record emphasized the frequency with which relevant foods were eaten and estimated the quantities of potentially fortifiable foods consumed; in addition, the reasons for not eating foods rich in vitamin A and carotene were determined. The nutritionist also assisted the team leader (ophthalmologist) in checking the completeness and standardization of survey forms. In this way, errors and inconsistencies could be detected immediately and corrected before the team moved on to the next sample site.

Problems in Data Analysis and Coverage

To expedite data analysis, all forms 40 and 41 were first cleaned, edited, and matched. According to family data recorded on form 40, there were 21,391 families containing 36,701 children who were eligible for inclusion in the study. Among these, 36,060 children (98 percent of the total) from 21,349 families (99 percent of the total) were examined (form 41NX). All 36,060 children examined were included in the calculation of prevalence rates.

Correlations, including dietary and anthropometric data, also required the use of form 42NX. When the information on these forms was matched with the data on forms 40 and 41, 2 percent of the 35,274 children (700) were found to have incomplete records. When these 700 children were identified, we found that their cards 42 had not been punched. Except for 230, all of whom came from three villages (two in Central Java; one in West Java), the remainder were evenly distributed among the other sample sites. Age and sex distribution of the total (36,060) and reduced (35,274) samples were identical. None of the missing children were abnormals, matched controls, or part of the random sample.

Of the 72,120 eyes examined, 649 were diagnosed as having Bitot's spots (X1B). These diagnoses were cross-checked against the presence

of dryness and foam. In 14 (an insignificant 0.02 percent), the description was incompatible with the diagnosis: about half represented overdiagnoses (7 out of 649, or 1 percent of all Bitot's spots) and half represented underdiagnoses (0.01 percent of all normals). The total number of cases of Bitot's spots (category X1B) identified in the survey was 358. Because a control matched for age and sex was not always available at the sample site, the number of matched controls (340) was slightly smaller than the number of cases of Bitot's spots.

IV. MAJOR FINDINGS AND THEIR IMPLICATIONS

Data collection in all studies was completed in January 1979, as scheduled. Analysis proceeded along with collection. When deemed useful, preliminary results were described in periodic Interim Reports and a Project Termination Report.[14] This section reviews, amplifies, and updates the findings pertinent to the major obstacles posed in Section I. Findings are organized by topic rather than by individual study: in other words, the results of all studies bearing on the same point are presented together.

More detailed computer analyses, which are beyond the scope of this report, are on file at Indonesia's National Center for Health Research and Development. Interested and qualified individuals can gain access to them by applying to the Center's Director.

A. Clinical Classification of Xerophthalmia and the Role of Vitamin A Deficiency in Its Etiology

Night Blindness

Experiments on adult human volunteers suggest that night blindness is the earliest clinical manifestation of vitamin A deficiency.[15] Our findings suggest that this is also generally true among young children assessed under natural field conditions.

During the first clinical round of Study I, when serum levels of vitamin A were determined, 325 children had xerophthalmic lesions of the conjunctiva or a history of night blindness. As shown in Table 1, twice as many had a history of night blindness (with or without conjunctival lesions) as had conjunctival lesions (with or without a history of night blindness). The mean serum levels of vitamin A (see Table 2) and the proportion of cases with "adequate" levels of vitamin A among children with isolated night blindness was slightly higher than among children with either isolated conjunctival lesions or a combination of the two ($P < .05$ by linear trend).[16] The serum levels of vitamin A among normal, matched controls in the neighborhood and those in the random subsample were substantially higher.

Among 210 children who had a history of night blindness objectively tested in the field, 97 percent were found to be night blind. It is interesting to note that the mean serum levels of vitamin A among children with positive and negative tests were identical (13.7 ug/dl), suggesting that the parent's history was more accurate and sensitive than was the crude field test. Some children with positive histories, especially those with negative tests, were said to be night blind only after a photic stress such as flying a kite on a sunny day.

The results of Study III support these findings. Eighty-nine percent of the patients whose conjunctival lesions responded to vitamin A had a positive history of night blindness, whereas 75 percent were shown to be night blind on objective assessment. In contrast, among nine patients with unresponsive lesions, only three had a history of night blindness, and none were night blind when tested (see Table 3).

An additional 21 children presented in Study III had a history of night blindness in the absence of conjunctival disease (excluding two cases of retinitis pigmentosa and one of Best's disease). Only 12 of these 21 children proved to be night blind by objective assessment and probably suffered an earlier, milder form of night blindness than did those who already had conjunctival lesions, which often were apparent only after a photic stress. In fact, one child was said to be night blind only after watching "too much television"--an interesting commentary on the lack of association between determinants of vitamin A deficiency and economic advancement.

In most children, night blindness usually disappeared within 24 to 72 hours after vitamin A therapy.

Conjunctival Xerophthalmia

The World Health Organization's (WHO's) classification of xerophthalmia (see p. 94) distinguishes among (1) conjunctival xerosis, X1A, which is ambiguously defined as a variable combination of dryness, thickening, wrinkling, and pigmentation, (2) Bitot's spots that lack conjunctival xerosis and, by implication, are unrelated to vitamin A deficiency, and (3) Bitot's spots in the presence of conjunctival xerosis, X1B. Careful examination of patients in Studies II and III indicated that these divisions are both arbitrary and misleading and that the extent of conjunctival involvement is of greater significance.

Fifty-nine of the 83 patients who had conjunctival lesions in the absence of obvious corneal involvement received vitamin A therapy and were followed closely. All but 9 responded to some extent (see Table 5). Responsive lesions were defined as demonstrating resolution or cure within two months after the first massive dose of vitamin A; unresponsive lesions, as remaining unchanged for at least three months after the first massive dose (all 59 children received at least one, and often two, additional doses as well). As illustrated in Tables 6 and 7, responsive lesions almost invariably began to disappear within one week after treatment, although they took somewhat longer to disappear completely. Not surprisingly, initial serum levels of vitamin A in children with responsive cases were lower than in the unresponsive cases (see Table 8).

There was no difference in the clinical appearance of lesions that responded to vitamin A and those that did not. In all instances, the basic lesion was a dry, granular, unwettable patch of conjunctiva aptly described as looking "like sandbanks at receding tide." Under the slit lamp, these lesions had a bubbly appearance. Bitot's spots simply represented larger, more compact, and confluent bubbles. Pigmentation, wrinkling, and thickening were difficult to define and were present in a large proportion of normal children. The vast majority of responsive and unresponsive lesions occurred bilaterally: 92 and 78 percent, respectively.

Although the clinical appearance of responsive and unresponsive lesions was identical, the following differences were useful in distinguishing the two groups of patients:

- In every eye in which a lesion was present, whether or not the lesion responded to vitamin A, the area adjacent to the temporal limbus was involved. In contrast, nasal lesions were distinctly more common among affected eyes in responsive cases: 64 percent versus 6 percent, respectively ($p < .001$; see Table 9).
- Children with vitamin A deficient, responsive lesions were significantly younger than those with unresponsive lesions (see Table 10). Among preschool-age children, only 3 percent of the cases failed to respond to vitamin A. Among children age 10 or older, however, 60 percent of the cases failed to do so ($p < .001$ by linear trend; see Table 11).
- As indicated earlier, night blindness--as determined by history and examination--was significantly more common among vitamin A-

deficient patients with responsive lesions (87% by history and 73% by examination) than among patients with unresponsive lesions (33% by history and 0% by examination) ($p<.001$; see Table 3).

Although the origin of the unresponsive lesions remains uncertain, a substantial proportion probably represent sequelae of old, healed xerophthalmia. This conclusion is based on the following factors:

Age. Patients with unresponsive lesions were significantly older than vitamin A-deficient patients with active lesions (see Table 10).

Duration of lesion. Patients with unresponsive lesions were twice as likely to report that their lesions had been present for at least two months (5 out of 28 responsive patients versus 4 out of 8 unresponsive patients for whom histories were available) and that they had experienced a prior xerophthalmic episode (4 out of 50 responsive patients versus one-third of the unresponsive ones). These differences, however, were not statistically significant.

Susceptibility of temporal quadrant. Perhaps the major evidence lies in what seemed to be the temporal quadrant's peculiar susceptibility to keratinizing metaplasia induced by vitamin A deficiency. As noted earlier, unresponsive lesions were essentially limited to the temporal quadrant. Although the temporal quadrant was invariably involved in responsive cases, the nasal quadrant was also involved in a large proportion of them. Hence temporal involvement, even in responsive cases, was more common, never less common than nasal involvement.

In these cases, the temporal quadrant was often more severely affected than the nasal quadrant, never less severely affected ($p < .001$; see Table 12). Additionally, the temporal lesions often healed more slowly than the nasal lesions, never more quickly. Among seven responsive (uncured) cases that presented with both nasal and temporal lesions, the nasal lesions disappeared in all, while the temporal ones always persisted, although in reduced form. Examined at that point, they would mistakenly appear to be classical nondeficient, unresponsive cases. Among six cases in which nasal and temporal lesions disappeared with therapy, but at different times, the nasal lesions always disappeared first. In no case did the temporal lesions disappear before the nasal lesions.

Histopathologic studies tended to confirm this interpretation. In

unresponsive cases, the histopathologic abnormalities (keratinization, loss of goblet cells, and maturational disorganization) were limited to the clinical lesion itself. In responsive cases, these changes involved all the bulbar conjunctiva, representing the generalized metabolic disturbance induced by active vitamin A deficiency.

Finally, unresponsive lesions did not recur after total surgical excision.

Taken together, these clinical and histopathologic findings suggest that vitamin A deficiency induces a chronic, self-perpetuating metaplastic change confined to the temporal limbus. The more extensive the conjunctival involvement, the more severe the disease. As described above, temporal involvement may or may not be accompanied by active vitamin A deficiency, whereas involvement of both the temporal and nasal quadrant almost always is accompanied by deficiency. More extensive conjunctival involvement suggests the presence of established or incipient corneal disease. In only three (6 percent) of the 50 noncorneal, responsive cases did the conjunctival lesions extend outside the temporal and nasal quadrants. In one case, the cornea was already covered by densely staining, superficial punctate lesions (see the description of case #200/011 below). In contrast, in 50 out of 106 eyes (47 percent) in cases with obvious but mild corneal disease (X2), the xerosis involved 180° or more of the bulbar conjunctiva, usually inferiorly, while in 12 of the 50 eyes, the entire bulbar conjunctiva was dry, unwettable, and often skin-like in appearance.

One interesting clinical finding, which, unrecognized, has led to considerable confusion in the past, is that active corneal disease related to vitamin A deficiency can occur in the absence of clinically apparent conjunctival xerosis. At least two mechanisms account for this phenomenon. The less common one, in our experience, is a rapid deterioration in vitamin A status, which can lead to changes that are clinically apparent in the cornea before they appear in the conjunctiva. This chain of events was well documented in a single case (#200/011), a severely malnourished 2-year-old boy who had extensive, severe conjunctival and corneal xerosis and a unilateral corneal ulcer. All his ocular abnormalities responded rapidly to massive vitamin A therapy and disappeared within ten days, but his mother refused to hospitalize

him. When seen again two weeks later, his general nutritional status was even worse: both legs were grossly edematous, and he had severe corneal xerosis and small ulcers bilaterally. His conjunctiva, however, was clinically normal. The corneal changes responded promptly to vitamin A therapy, but the child died three days later. A similar pattern was observed in another 2-year-old boy (#200/068) in the absence of ulcers.

The more common mechanism relates to the effect of conjunctival injection and corneal destruction (the two tend to occur together) on the presence of clinically recognizable conjunctival xerosis. The best demonstration of this effect appears in Table 13. Twenty individuals enrolled in Study II had conjunctival xerosis in one eye but not the other. Conjunctival injection (hyperemic, nonpurulent inflammation) was observed in 5 of the 20 eyes with conjunctival xerosis but in 19 of the 20 eyes without it. In 15 cases, the nonxerotic eye was inflamed while the xerotic one was not; in four cases, both eyes were inflamed; and in one case, the xerotic eye was inflamed while the nonxerotic one was not ($p<.001$).

Similar results were obtained in relation to corneal destruction: among 16 of 17 cases with necrosis in at least one eye, the necrosis was either more severe or present only in the eye with the nonxerotic conjunctiva ($p < .001$). This paired analysis of discordant eyes eliminated systemic variables such as differences in general nutritional status and vitamin A status.

Delineation of these two mechanisms helps to explain earlier observations of corneal destruction in the absence of conjunctival xerosis and should eliminate some of the confusion over the role of vitamin A deficiency in these cases.

Study I confirmed, under unbiased field conditions, the association between active vitamin A deficiency and Bitot's spots in young children. Ninety percent of the children in whom Bitot's spots were observed during the first clinical round had serum vitamin A levels below 20 ug/dl (see Table 2). Similarly, in almost 80 percent of children who had Bitot's spots during the seventh round and were given a high-potency capsule, the lesions completely disappeared within two or three weeks (see Table 14). This contrasts with the rate of spontaneous cure (50 percent)

found among recipients of low doses ($p < .05$). The proportion associated with active vitamin A deficiency was probably higher than the 80 percent cure rate among recipients of large doses suggests. Among the eight uncured patients, two originally had both temporal and nasal lesions. In both cases, the nasal lesions disappeared after therapy but the temporal ones persisted. This finding is consistent with the results of Study III, where it was found that temporal lesions often took longer to disappear than did nasal ones. By adding just these two responsive cases, the rate of unresponsiveness among recipients of large doses in the eighth clinical round was reduced to 16 percent. Since a significant proportion of temporal lesions will regress without actually disappearing during two to three weeks of follow-up (see Study III), it is likely that additional uncured subjects (who had temporal lesions alone in the seventh round) responded as well and that the true rate of unresponsiveness was even smaller.

The results of Study III and those of rounds 1, 7, and 8 in Study I are remarkably consistent and suggest that at least 90 percent of preschool-age children with Bitot's spots suffer from active, clinically significant vitamin A deficiency.

The low historical cure rate of 80 percent among night blind children treated with a massive dose is surprising (see Table 14). There are at least two possible explanations for this: mothers may have been more alert to the presence of night blindness than to its disappearance, and some mothers--having received attention for their night blind children once--may have responded in a way which they believed was most appropriate to ensure that their child would receive additional treatment. The supposition that some children said to be night blind no longer were is supported by the fact that a number of them had responsive temporal and nasal Bitot's spots.

Corneal Changes

It has traditionally been assumed that corneal xerophthalmia follows conjunctival changes. Results of Study III indicate that the cornea is affected much earlier and at higher serum levels of vitamin A than was previously supposed. Early analysis demonstrated that 60 percent of the cases with confirmed, isolated night blindness (X1A) and 75 percent of

the cases with conjunctival xerosis considered to be free of corneal involvement (X1B) during routine examination with a hand light already had been diagnosed as having fluorescein-positive superficial punctate keratopathy during a slit-lamp examination (see Table 15). In contrast, punctate keratopathy was present in only 7 percent of the matched controls (some of whom may have had subclinical vitamin A deficiency). The punctate keratopathy disappeared rapidly after massive vitamin A therapy (see Table 16), whereas it either remained the same or became worse in children who received low doses (which explains why the use of low-dose controls was discontinued in Study III). This is the earliest clinical corneal change in xerophthalmia reported to date.

In its earliest and mildest form, the punctate keratopathy was limited to the inferonasal quadrant. When the disease became more extensive, the lesions became denser and spread upward and temporally, eventually covering the entire cornea. Stromal edema usually ensued at this point, and during examination with a hand light, the corneal involvement was grossly apparent.

With experience, it was possible to recognize corneal involvement with a hand light much sooner than was previously described: i.e., as a loss of luster beginning near the inferior limbus. This involvement does not appear, as previously supposed, to be secondary to loss of mucous-producing goblet cells with attendant disturbance of tear film and local drying.[17] Our histopathologic studies demonstrated that goblet cells do not begin to return until after the punctate keratopathy begins to clear (see Table 17).

Because of the number of cases and the careful observations that were possible, most information on the clinical characteristics of corneal involvement was derived from Study II. Among 162 consecutive children with gross corneal involvement suggesting active xerophthalmia (see Table 18), only 11 who came to the clinic with active corneal disease were excluded from this series because other etiologies were obviously involved: four cases of neonatal ophthalmia, all less than 3 weeks old with grossly purulent eyes and positive cultures and smears; three cases of phlyctenulosis; two classical cases of epidemic keratoconjunctivitis; one mild case of measles keratoconjunctivitis; and one "classical" case

of multiple peripheral ulcers hypersensitive to staphylococcus that cleared up with steroids and topical antibiotics. Also excluded were four patients who had received antibiotics and vitamin A before appearing at the clinic and whose cases had already begun to resolve and two patients with active measles and stromal lesions, atypical for xerophthalmia (both patients were deficient in vitamin A and are discussed later).

Corneal abnormalities among the 162 patients in the series varied from minimal haziness to complete dissolution. The mildest change was a haziness or lack of luster, usually first noted adjacent to the inferior limbus. When involvement was more severe, the entire corneal surface was affected and often had a dry, "pebbly" appearance. More than 90 percent of these cases had gross corneal involvement bilaterally, and more than half exhibited stromal edema (the cornea was estimated to be at least 1.5 times thicker than normal). In its most severe form, the xerotic cornea was covered with an obviously thick, peeling layer of keratinized epithelium.

Corneal (stromal) destruction classically began as a round, punched-out ulcer of variable diameter--as if a trephine or cork borer had been applied to the eye. These ulcers could be partial or full thickness and usually were free of any evidence of infiltration. Larger, more irregular ulcers, usually of full thickness, may have represented the end result of the same process or the sloughing of large localized areas of corneal necrosis. These areas of necrosis looked like abcesses but did not provide clinical evidence of surrounding infiltration. Except for being localized, usually to the inferior quadrant, this picture was identical to that of full-thickness, limbus-to-limbus corneal dissolution, the severest manifestation of the disease.

With treatment, corneal xerosis disappeared entirely; small ulcers (1 to 3 mm in size) healed, often without any evidence of scarring; and larger ulcers and abcesses scarred, healing as leukomas or, if perforated, as adherent leukomas. Full-thickness, limbus-to-limbus necrosis scarred over slowly, if at all, and the eye invariably was lost.

All 162 presumptive cases of nutritional keratopathy were separated, purely on the appearance of the most severely affected cornea, into

the following clinical classifications grouped by likely pathophysiologic changes (see Table 19):

File	Classification	Degree of Pathology
1	$X2_1$	Mild xerosis: Haziness and loss of luster
2	$X2_2$	Moderate xerosis: Frankly dry, pebbly appearance
3	$X2_3$	Severe xerosis: Placque-like, keratinized surface
4	X3A	Small ulcers: Sharply demarcated and 1-3 mm in size
5	$X3_{A/B}$	Larger ulcers: Often full thickness and likely to be the end result of either small ulcers or localized stromal necrosis
6	$X3B_1$	Localized stromal necrosis
7	$X3B_2$	Unilateral corneal necrosis: Limbal to limbal
8	$X3B_3$	Bilateral corneal necrosis: Limbal to limbal

The only uncertainties arose when distributing some of the cases between files 4 or 5 and 5 or 6. Some cases lacked obvious conjunctival changes. Almost invariably they involved stromal destruction or conjunctival inflammation, either of which masks or reverses conjunctival xerosis, as mentioned earlier.

The vast majority of cases (82 percent) occurred in children ages 2 through 5 (median age, 3; see Table 19). The youngest cases was a 1-month-old boy with severe bilateral xerosis and complete dissolution of one eye. His mother, whose serum level of vitamin A was 13 ug/dl (she was free of clinical disease) claimed that the child had Bitot's spots at birth. The oldest patient in the series was 12 years old. The oldest patient encountered (just before the formal study was initiated) was a 24-year-old woman who had extensive conjunctival, corneal, and retinal involvement.

The proportion of very young children (under age 2) was directly related to the severity of corneal involvement ($p < .001$ for linear trend; see Table 20). Although this sample was obtained in a clinic and therefore was not necessarily a representative one, it suggests that

interventions aimed at children age 1 or older will miss only a small proportion of all cases of corneal disease but will miss a much larger proportion of the severest cases.

There were slightly more males than females in all categories: on average, males accounted for 53 percent of the cases.

It has been suggested that the corneal ulceration and melting described here may actually result from general malnutrition/protein deficiency, or local bacterial infection.[18, 19] The vitamin A, protein, and general nutritional status of these cases as well as the results of bacterial and fungal cultures and the response to therapy all suggest otherwise--that vitamin A deficiency was the specific final common pathway and the sine qua non of corneal (stromal) destruction in essentially all instances.

Within the limitations described below, all patients with corneal disease were deficient in vitamin A, and the more severe the disease, the more severe, on average, was the deficiency.

A number of difficulties preclude us from arriving at a precise estimate of vitamin A status in every case. First, the equipment failures described in Section III prevented the analysis of vitamin A and holo-RBP levels in some subjects. Fortunately, however, different equipment failed at different times; thus almost all cases are represented in one analysis or the other. Second, some patients received vitamin A before joining the study. In most instances this treatment consisted of an oil-miscible injectable preparation that had little affect on serum levels, but among them were two cases with the highest levels included in file 7 (12 and 13 ug/dl) and one case included in file 4 who had the highest level in the entire series (21 ug/dl). Two additional cases included in file 8 were known to have received oral doses of vitamin A (which has a marked affect on serum levels) and were therefore excluded from the analysis. Third, there was always the possibility that errors occurred in the laboratory, even when equipment failure was not recognized, and that some cases received oral therapy without our knowledge. We suspected that this occurred in two cases: one case, in file 6, whose serum level of vitamin A was five standard deviations from the mean but still below 20 ug/dl (17 ug/dl) was included in the analyses. The other (file 7), who was grossly out of range (32 ug/dl --

six standard deviations from the mean, and higher than any value observed among cases of Bitot's spots or among normal matched controls) was excluded from the analyses. Fourth, while serum levels of vitamin A and holo-RBP are the only practical means of establishing vitamin A status, they are merely a reflection of vitamin A stores, and not always an accurate one.

Despite these limitations, biochemical results in this series were in good accord with our clinical observations and deductions.

Mean serum levels of vitamin A were severely depressed for all categories of corneal disease (see Table 21), and the more severe the disease, the more severe the depression ($p < .01$). This suggests that the difference in vitamin A status probably accounts, at least in part, for the severity of the corneal involvement. The distribution of serum vitamin A levels shown in Table 22 suggests that, in our laboratory at least, gross corneal involvement was unlikely to occur at levels above 15 ug/dl. Fully 75 percent of all corneal cases occurred at levels below 10 ug/dl; only one-third of all cases of Bitot's spots and less than 10 percent of randomly sampled children in Study I fell below this level (see Table 2). The serum level of only one corneal patient with pure xerosis (X2), who received an oil-miscible injection before joining the study, was above 20 ug/dl, and that was at the borderline value of 21 ug/dl.

Holo-RBP levels confirm the severe depression of circulating, active retinol among patients with active corneal disease (see Table 23 and Figure 1).

The primary importance of vitamin A deficiency in the genesis of these lesions is confirmed by our therapeutic trials. Obviously, it was unethical to withhold treatment for protein/general malnutrition or severe systemic disease from any child with corneal disease. Nonetheless, a number of parents refused to hospitalize their children. In general, these children could only receive vitamin A therapy and immediately returned home to their regular diet. Their response to isolated vitamin A therapy confirms our supposition that vitamin A deficiency was the sine qua non of corneal destruction. Among 22 cases of active corneal disease, 11 with ulcers or local necrosis and 10 with severe protein-energy malnutrition (including seven with pitting edema),

one died and two were ultimately hospitalized. But before this occurred, all 22 had begun to respond, with much the same time course as those who were hospitalized at the initial examination.

Although most children with corneal involvement were malnourished, a significant proportion were not. The degree of wasting (measured as percentage of standard weight for height)[20] was directly related to the severity of corneal disease ($p < .02$ for linear trend; see Table 24). But fully 8 percent of those in files 7 and 8 had a weight for height that was at least 90 percent of western standards, and over a third, 80 percent or more. Almost half the children with localized necrosis (file 6) and two-thirds of those with less severe disease, including ulcers (files 1-5), had a weight for height that was at least 80 percent of western standards.

Kwashiorkor, as evidenced by gross pitting edema, was recorded for 29 percent of the 157 corneal cases (see Table 25). The rate was especially high among cases of total corneal necrosis (files 1-6 versus 7-8; $p < .05$).

Measurements of serum albumin (Tables 26 and 27) and transferrin (Tables 28 and 29) are in close agreement with these results. Mean serum albumin and transferrin levels were inversely proportional to the severity of the disease; this was especially evident in the difference between the severest forms of disease (files 7-8) and the remainder ($p < .01$). In a significant proportion of all severe cases, serum albumin levels were in the normal range ($\geq$ 3.5 gms/100 ml), although the proportion of severe deficiencies ($<$ 2.0 gms/100 ml) was far greater among those with the severest disease (files 7-8).

The increased prevalence of generalized malnutrition and protein deficiency among cases of corneal involvement, especially of the severest sort, may simply indicate that those with the lowest intake of vitamin A were also likely to have the lowest intake of food and protein. Results of additional therapeutic trials, which will be discussed later, suggest that the situation is more complex: that severe generalized malnutrition, especially protein deficiency, interferes with utilization of vitamin A and thereby may potentiate the effects of inadequate vitamin A intake and so precipitate or exacerbate clinical xerophthalmia.

Because the clinical prevalence of other nutritional deficiencies

(cheilosis, stomatitis, and the like) was rare, they appear to play little or no role in the corneal abnormalities observed. Furthermore, local bacterial or fungal infections probably do not contribute to corneal ulceration or melting in more than a tiny proportion of cases. The results obtained from the formal, controlled therapeutic-diagnostic trial with topical antibiotics were inconclusive because most cases required systemic antibiotic therapy for other conditions such as tuberculosis, infections of the respiratory tract, and gastroenteritis. But because patients whose parents refused to hospitalize them were included outside the formal trial, data are available on 22 patients with ulcerated or locally necrotic corneas that were not exposed to either topical or systemic antibiotics. Healing was progressive and rapid in 20 of these 22 cases (90 percent). One of the remaining two cases involved an ulcer (X3A) that was larger when seen again four days later, but it began to resolve by the sixth day. The other patient (# 200/080), who had identical, small inferior ulcers in both eyes during the initial examination, was part of the formal trial. By the third day, the ulcer treated with an antibiotic had clearly improved, while the ulcer in the untreated eye had become worse. Although the response of the untreated corneas in both cases was consistent with the overall proportion of treated eyes that did poorly at first, the formal trial was discontinued. The only organism cultured from the untreated eye in the second case (#080) at the time it deteriorated was a coagulase-negative micrococcus albus. The child was severely malnourished, with a weight for height that was 65 percent of standard and a serum transferrin of 35 mg/dl.

Bacterial cultures of conjunctival and corneal swabs and scrapings (the latter only from ulcerated or necrotic corneas) obtained during the initial examination grew a wide variety of organisms. Potentially, the most pathogenic were Pseudomonas, coagulase-positive micrococcus aureus, and E. coli. There was no significant difference in the prevalence of positive cultures, for any or all of these organisms together, between the various forms of corneal involvement or between all abnormal corneas as a whole and 50 eyes of normal controls (see Table 30). Paired comparisons (not shown) between ulcerated and nonulcerated eyes of the same patients (n = 33) also failed to reveal any differences. "Other

organisms," which included strains of Haemophilus, Streptococcus viridans, Diphtheroids, and Aerobacter were common in all groups. Proteus was cultured from a single eye with corneal xerosis. Fungi, which may have been contaminants, grew in cultures from 17 eyes: Candida,[2] Penicillium,[12] and Aspergillus.[3]

Retinal Changes

Typical white retinal lesions were observed in a significant proportion of cases in which they could be sought (vitamin A responsive X1 and X2; see Table 31). They were more common in older individuals and in those with more severe deficiencies and tended to disappear slowly (over two to four months) after vitamin A therapy. Special visual field and fluorescein angiographic studies on the 24-year-old woman indicated that these lesions were not, as previously supposed, white bumps or dots in the retina but widely and diffusely depigmented areas deep within the retina or in the retinal pigment epithelium. They tended to spare the posterior pole* and probably represent disruption of the retina's outer segments, as suggested by the absolute scotoma found to conform precisely to the distribution of these lesions.

B. Therapy

Systemic Vitamin A

It has been recommended that treatment of active xerophthalmia should be initiated with an immediate injection of 100,000 IU of water-miscible vitamin A.[10] But there are several practical drawbacks to this scheme: (1) water-miscible vitamin A is less stable than are oil-miscible oral preparations, (2) it is more expensive and requires needles and syringes, (3) experienced workers trained in strict, sterile techniques must administer it, and (4) water-miscible injectable vitamin A is unavailable in Indonesia and is in short supply throughout the world.

Therapeutic trials conducted on corneal cases enrolled in Study II indicated that oral doses of oil-miscible vitamin A are just as effective as injections of the water-miscible form. In an early series, patients

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*The term posterior pole, the back of the eye, usually pertains to the area surrounding the optic disc nasally and the superior and inferior vascular arcades temporally and thus includes the macula (the area of sharp vision used in reading).

received either one oral dose of 200,000 IU of oil-miscible vitamin A or an injection of 100,000 IU of water-miscible vitamin A. Because both regimens resulted in either delayed healing or early relapse in a significant proportion of severely malnourished children, the trial was changed and an additional oral dose was given to all patients the day after initial therapy. This reduced the number of early relapses and refractory cases.

When supplies of water-miscible injectable vitamin A were exhausted, masking was maintained by giving the parenteral group 200,000 IU of oil-miscible vitamin A in divided doses instead--the generally accepted treatment for xerophthalmia in Indonesia at that time. These recipients are excluded from the analyses, which accounts for the larger number of oral-oral than (water-miscible) parenteral-oral recipients in the comparisons. Because eyes with limbal-to-limbal necrosis could not possibly heal, they were excluded from the clinical evaluation.

The double-dose treatment groups, oral-oral and (water-miscible) injectable-oral, were comparable in all major criteria that were expected to influence clinical outcome (see Table 32). As shown in Table 33, clinical response to the two treatment regimens was identical, even when analysis was limited to cases with active diarrhea or protein-energy malnutrition (see Tables 34 and 35).*

Consistent with previous reports, serum vitamin A reached higher levels in the parenteral group (see Table 36).[21] But serum "vitamin A" levels represent at least two major substances: retinyl esters, the physiologically inactive form in which the vitamin is administered; and physiologically active retinol-binding protein (holo-RBP). As can be seen, serum holo-RBP levels were virtually identical in the two groups at every interval, which confirmed the clinical observations. The only borderline statistically significant (and clinically insignificant) difference occurred at 24 hours.

Severe protein-energy malnutrition had a significant effect on the response to both regimens. In every instance, patients who responded

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*Active diarrhea was defined as four or more loose stools per day. The diagnosis of protein-energy malnutrition was based on one or more of the following: serum albumin < 3.0 gms/dl or transferrin < 50 mg/dl; weight for height < 70 percent of standard; pedal edema.

slowly were severely malnourished. In addition, the magnitude of biochemical response at four and 24 hours was directly related to initial protein status ($p < .05$; see Table 37 and Figure 2). Recipients of both single and (ultimately) double doses are included in this comparison. During the period of vitamin A deficiency, patients with low serum levels of albumin or transferrin (not shown in Table 37) apparently synthesized and stored less retinol-binding protein than did better nourished patients. Therefore, they were less able to respond to administration of vitamin A with an outpouring of holo-RBP from the liver. Nevertheless, most did respond clinically, as mentioned earlier. In two severely malnourished patients already described (#200/011 and #200/068), however, the clinical remission proved to be transient: both patients relapsed within two to four weeks.

Isolated vitamin A therapy seems to be capable of reversing the xerophthalmic process, even in severely malnourished children. But to maintain the remission--not to mention save the child's life--it may be necessary to correct the underlying protein deficiency and administer frequent, periodic, and massive amounts of vitamin A. This perhaps explains, in some cases, the association between severe corneal pathology and protein-energy malnutrition discussed earlier.

In no instance did we observe symptomatic toxicity as a result of either double-dose regimen, although a small percentage of patients developed asymptomatic, transient papilledema. When a 3-month-old malnourished, nonxerophthalmic child inadvertently received high-potency capsules on two successive days, he did not develop papilledema, but there was some increased fullness and bulging of his open fontanelle, which suggested that the papilledema in the other cases represented a mild, transitory subclinical increase in intracranial pressure.

These findings are potentially significant because they suggest that any mother or health worker can provide optimum vitamin A therapy by using readily available, inexpensive, safe, and effective oral capsules.

Because oral therapy alone is as effective as parenteral plus oral therapy and because double-dose therapy fails to eliminate the problems encountered among severely malnourished children, it seems reasonable to recommend three oral doses--one on admission, another the

following day, and a third after one or two weeks (this particular regimen was not actually tested).

The fact that malnourished children have difficulty utilizing and storing vitamin A emphasizes the need to correct their other nutritional problems during treatment.

Topical Retinoic Acid

Despite maximal systemic vitamin A therapy, corneal healing was often delayed from two to four days, and the cornea occasionally deteriorated in the interim. In part, this may have been the result of a delay in delivering sufficient amounts of physiologically active vitamin A to the outer eye. Therefore, trials were carried out to determine the value of adding topical retinoic acid (0.1 percent in arachis oil) to the therapeutic regimen as a method of bridging this critical period.

In fact, application of retinoic acid three times a day proved to be a safe and effective method of speeding corneal healing. None of the preliminary trials produced any adverse affects. In four early cases having symmetrical corneal involvement in both eyes, the eye treated with retinoic acid healed faster than the one given a placebo. Studies on later subjects confirmed these results, but they also indicated that ulcers treated with retinoic acid occasionally healed with greater scarring. In only one of these additional cases did the eye given the placebo deteriorate to a significant, visually disabling degree. Although undoubtedly of value in selected cases (with nonaxial ulcers, or for one eye of a patient with axial ulcers in both eyes) treated in sophisticated facilities, retinoic acid is probably not a practical therapeutic agent to use under field conditions.

C. Magnitude of the Problem: Prevalence and Incidence

True estimates of the magnitude of xerophthalmia require carefully executed, prospective, longitudinal field studies. To our knowledge, Study I is the only one that is large and comprehensive enough to provide reasonably accurate rates of incidence for corneal involvement. Surveys of prevalence such as Study IV have been carried out in a number of countries, but these only provide estimates of the number of cases at a particular time, not the number of cases that occur over a given period (e.g., one year).

Because it is logistically impossible to carry out a longitudinal study on a representative sample of an entire population, especially a population as large and dispersed as Indonesia's, a longitudinal study (Study I) was carried out in one area instead. The rates of incidence were then extrapolated to other areas of the country according to the degree that prevalence rates in these other areas (obtained during Study IV) approximated the prevalence in the longitudinal study area (averaged over the first year, the time interval used in calculating incidence).

It must be emphasized that the incidence observed in Study I is a minimal rate. Children were examined only once every three or four months; consequently, those who developed and spontaneously recovered from mild corneal disease and those who died with severe corneal disease between examinations were unrecognized. Additionally, the mere presence of the survey teams, the treatment and hospitalization of all early corneal cases, and the treatment and the encouragement to seek additional help for ill and severely malnourished children that parents received certainly must have reduced the incidence and severity of xerophthalmia in the study population. Furthermore, both Study I and Study IV were limited to preschool-age children (under age 6). Although these children undoubtedly account for the vast bulk of xerophthalmia cases, the age range of patients seen in Study II (see Table 19) indicates that a substantial portion were older and would have been missed. Finally, the clinic and hospital-admission data and results of Study I suggest that the countrywide survey (Study IV) was carried out during the season in which xerophthalmia is least prevalent.

Study I: Incidence and Prevalence of Corneal and Noncorneal Disease

The incidence (number of new cases) of active corneal xerophthalmia in the longitudinal study area was astounding (see Table 38). Two estimates are included for the 12-month period encompassed by clinical rounds 2 through 5 conducted from July 1977 through June 1978. The first round provided the baseline population of children who were free of corneal xerophthalmia. The higher estimate--5.8 per 1,000 per year ($CI_{95\%}$ 3.0 - 8.6 per 1,000 per year)--is based on a strict definition of the denominator of "at risk" children. This denominator includes, for each round, only those children who were examined during that round and had also been examined and were free of corneal disease during the

immediately preceding round. The denominator shown in Table 38 is the average number of such "at risk" children examined in each of the four rounds (2-5).

The denominator used to calculate the lower rate--3.5 per 1,000 per year ($CL_{95\%}$ 1.8 - 5.2 per 1,000 per year)--represents the average number of children enrolled in the study and hence eligible for examination during each of the four rounds, whether or not they were ever examined.

The reason for providing two estimates is that the measurable rate (as opposed to the true rate, which would also include children with mild cases that cured spontaneously and children with severe cases who died between rounds) probably lies somewhere in between. The higher rate assumes that children who were not examined had the same rate of disease as those who were. It could be argued that children with active corneal disease were more likely to be at home and therefore examined than were children without corneal disease and that the higher rate is biased by this differential coverage as a result. But the opposite could also be true: that even the higher rate is a biased underestimate because sick children were sent to hospitals or were otherwise hidden away from the team. The lower rate, which assumes that all unexamined children were free of disease, is certainly an underestimate.

A conservative approach is to assume that the measureable rate (as opposed to the true rate, which would be still higher for reasons already cited) lies between the two and is closer to the higher than the lower. Subtracting one-third of the difference between them from the higher rate gives an overall, conservative estimate of 5.0 per 1,000 per year ($CL_{95\%}$ 2.6 - 7.5 per 1,000 per year). At this rate, 3 percent (1.6-4.5 percent) of all children born into the study area would develop grossly evident corneal xerophthalmia before reaching their sixth birthday (0.5 percent x 6 years at risk).

There is no way of knowing how many of these 16 children would have gone blind if untreated. Five (31%) would almost certainly have gone blind or suffered severe, bilateral visual loss, and an additional three (19%) would have suffered unilateral visual loss. Among the remaining eight (50%), who had severe corneal xerosis, some might have gone blind, while others might have improved after receiving the treatment locally available or increasing their dietary intake of vitamin A.

Additional estimates of likely outcome are available and are in reasonable agreement with this estimate. During the first clinical round of Study I (which included areas subsequently dropped for logistical reasons), four children were diagnosed as having active corneal disease. Two (50%) definitely had existing or potentially blinding lesions (necrosis or large ulcers) bilaterally and an additional case (25%) unilaterally. The more severe disease encountered during this round suggested that corneal involvement had existed for more than two or three months in a significant proportion of cases. Since this was the first examination, the children had not been treated for milder disease during a preceding round.

For similar reasons, we would expect to find a comparable pattern in the countrywide survey (Study IV), and indeed we did. Among 22 children with active corneal disease, eight (36%) had large corneal ulcers or necrosis in both eyes, and an additional four (18%) had them in one eye. Four additional children (18%) had shallow ulcers or erosions in both eyes and one (5%) had them in one eye. Only six (27%) of the 22 children had intact, xerotic corneas.

Among the 162 cases enrolled in Study II, 29 percent had active bilateral corneal ulcers or necrosis. Although this rate is compatible with the rates discussed above, it is probably lower because parents who were concerned enough to bring their children to the clinic probably did so at a relatively earlier stage of the disease. In fact, many children were brought to the clinic because of night blindness or Bitot's spots, and consequently mild corneal xerosis was not discovered until the examination.

In all likelihood, the higher rates observed in Study IV and during the first round of Study I most accurately reflect what is actually occurring in the field. At a minimum, it appears that one-third to one-half of children with active corneal involvement are likely to go blind.

The fact that they need not go blind if treated appropriately is evident from the results of Study II. Central corneal clarity that was compatible with 20/20 vision was present, at discharge from the hospital, in the better eye of all cases in files 1-5, 93 percent of the cases in file 6; 82 percent of those in file 7, and none in file 8. Sophisticated surgical therapy appears to be unnecessary. Even when punched-out ulcers perforated, the defect invariably became plugged with

iris; thus the anterior chamber was preserved. The defect usually healed rapidly, on treatment, as an adherent leukoma. Since these lesions were usually peripheral, the pupillary axis--and vision--were frequently spared. In cases of limbus-to-limbus melting (keratomalacia), the entire cornea was necrotic, the anterior chamber was lost, and even if the facilities had permitted corneal transplantation, the effort probably would have proved futile.

The prevalence of active corneal disease in the area included in Study I was calculated simply by dividing the number of active cases diagnosed by the number of examinations performed. Each examination a child received was counted as one: e.g., if the same child was examined in each of four rounds, the number of examinations counted was four. Since this denominator is closer to the total number enrolled and is the only one available in Study IV for comparison, it is the one used. Similarly, since the goal is to extrapolate rates of incidence from Study I to Study IV by comparing their rates of prevalence, the prevalence listed in Table 39 represents the average for rounds 2 through 5, from which annual incidence was calculated in Study I. According to WHO, a prevalence of one case per 10,000 designates a significant public health problem. According to Table 39, however, the range of prevalence rates calculated in Study I was from 5 to 20 times higher than WHO's criteria, with a mean of 12. Since all children diagnosed as having active corneal disease were treated immediately, and therefore were not permitted to accumulate in the population, this prevalence is probably lower than it might otherwise be.

Rates of prevalence and incidence shown for noncorneal disease include cases of night blindness and conjunctival xerosis. Therefore, they are not comparable to WHO's criterion for Bitot's spots--the one used in Study IV. Hand-tabulated rates of incidence (new cases developed), cure (established disease that disappears spontaneously), and prevalence observed for each round are shown in Table 40.

The general drop in prevalence in succeeding rounds may signify a natural cyclical trend or indicate that the villagers simply became more conscious of the problem--and its prevention and cure--because of the team's work (especially between rounds 1 and 2). On the other hand, rates of incidence were relatively constant. At an annual rate of

incidence of 8.8 percent (the total quarterly rates for rounds 2 through 5), 53 percent of children residing in this area develop clinical xerophthalmia (night blindness or conjunctival xerosis) before they reach their 6th birthday. Undoubtedly, some cases were simply relapses, and the number of new children at risk of developing xerophthalmia was somewhat less.

As expected, the prevalence of vitamin A deficiency based on serum concentrations was considerably higher than the prevalence of frank clinical disease, at least during the first clinical round (the only one in which blood samples were collected regularly). (See Table 2.)

Study IV. Prevalence

Definitions. Our definition of (active) Bitot's spots was the same as the one used in WHO's criteria for a public health problem: i.e., foam overlying an area of conjunctival xerosis (X1B).[10] Although we used WHO's criterion, it is important to note that areas of true conjunctival xerosis but without foam, and some almost skin-like were present in large numbers of children. If these cases had been included in our analysis, the rates of conjunctival disease would have been approximately one-third higher.

Active corneal disease (X2/X3) was also diagnosed using standard WHO criteria. All cases had frank corneal involvement, which was obvious during examination with a hand light, and all but one were accompanied by severe conjunctival disease (the single exception had keratomalacia, X3B, and had recently received vitamin A).

Most difficult to assess was the likelihood that old corneal scarring was related to xerophthalmic corneal involvement. Without actually examining the eye during the active phase of disease, we could only surmise , from available data (clinical findings, age of onset, and history of concomitant malnutrition, worms, cough, fever, measles, trauma, and purulent discharge) what that original process was. Although we could never be absolutely certain about the cause of scarring in any individual case, we could (by applying reasonably strict, conservative criteria) feel certain that most children in a particular group did or did not have true corneal scarring secondary to xerophthalmis (XS).

All cases of corneal scarring were classified, on a scale of 0 to 4, by the degree to which available data supported a diagnosis of XS. This did not necessarily mean that cases in the lower rankings did not suffer xerophthalmic damage; it meant only that the history and clinical findings suggested the likelihood of another etiology. Each case was classified on the basis of all contributory data. Parameters strongly suggesting a xerophthalmic origin included the following: an age over 1 year; bilateral involvement; severe scarring, especially with evidence of perforation (adherent leukoma, phthisis, descemetocele, or staphyloma); absence of a reasonably certain history of trauma or purulent discharge (although appropriately aged children with bilateral perforation and a history of purulence were considered xerophthalmic since this rarely occurs from infection alone and since "apparently purulent" discharge was observed among Study II patients with classical xerophthalmia); and presence of severe malnutrition, diarrhea, fever, or worms at the time of active corneal disease.

A total of 151 children had some degree of corneal scarring; one case had active disease as well. Among these, 60 cases (group 0) were almost certainly related to other causes (primarily congenital, trauma, or neonatal ophthalmia). An additional 37 cases (group 1) could have been caused by xerophthalmia but were more likely the result of other diseases. Most of the seven cases in group 2 presented a classical clinical picture of xerophthalmia, but they either had a history suggesting that another etiology might have been present or had a history of measles with mild corneal maculae, which could conceivably have resulted without implicating the xerophthalmic process. Groups 3 and 4 (18 cases and 29 cases, respectively) were likely to have suffered xerophthalmic corneal destruction and served as the basis for our minimal, conservative estimate of XS.

Findings. Rates of prevalence for Bitot's spots with conjunctival xerosis (X1B), active corneal disease (X2/X3), and xerophthalmic scars (XS) are shown in Tables 41 through 43. As already discussed, the sample size was chosen to detect prevalence rates of X1B and XS considered by WHO criteria a significant problem on a zonal basis (see Table 41). This is the only table in which the geographic distribution of rates can be considered reliable. Because the prevalence was higher than originally anticipated, however, it is possible to examine

the potential distribution of rates by province within each zone. It should be understood, however, that when dealing with small numbers of cases, their apparent distribution may be misleading. For example, if we expect the rate of active corneal disease to be one per 10,000 (WHO's criterion) and encounter only one case among 5,000 children surveyed throughout all of Sulawesi, the fact that the single case came from South Sulawesi (see Table 42) does not mean that South Sulawesi has more disease than the other provinces in Sulawesi. On the other hand, certain provinces such as Lombok and Aceh have enormous rates of disease, often in all three categories (X1B, X2/X3, and XS). In these instances, it is likely that a high focus of disease actually exists.

For comparison, WHO's criteria for a significant public health problem include any one of the following: (1) a prevalence of X1B of 2 percent or higher, (2) a prevalence of X2/X3 of at least one case per 1,000, or (3) a prevalence of XS of at least 10 cases per 10,000. According to Table 41, every zone but rural East Java had a significant problem according to at least one of these criteria.

Prevalence of active corneal xerophthalmia is the single most important criterion for determining the magnitude of xerophthalmia. It establishes the severity of actual corneal disease--the major reason for concern about xerophthalmia--and unlike XS, the diagnosis can be made with reasonable certainty. Every one of the five "homogeneous" rural zones, excluding East Java, had rates of active corneal disease that <u>far</u> exceeded the WHO criterion: the range was from almost 3 times greater in Sulawesi to 14 times greater in Sumatra. Among the separate units comprising the sixth "composite" zone, the numbers of children examined were far too low to expect to detect active cases. Yet active cases were detected in three units: Lombok had a rate 21 times greater than the WHO criterion; Bali, almost 8 times greater; and Kalimantan, 5 times greater.

Similarly, the limited numbers of children examined in urban sites should have prevented detection of active cases. Nevertheless, one case (a rate of 10 per 10,000) was found among slum dwellers in Surabaya, the only case in East Java.

In part because of the small numbers of cases involved, none of the (rural) zonal rates, including those in the subunits of the

composite sixth zone, were significantly different statistically from the average for rural Indonesia as a whole (see below). Confidence limits for the prevalence rates within each area are shown in Table 44. Cluster and random-sample methods for estimating standard error yielded virtually identical results. Using the stratified sampling technique illustrated in Table 45, the mean prevalence of active corneal disease (X2/X3) in the surveyed rural area of Indonesia as a whole was calculated to be 6.4 $\pm$ 1.6 per 10,000. (P $\pm$ SE), and the 95% confidence limits were 3.2 - 9.6 per 10,000.

The prevalence of corneal scars (XS) believed to be secondary to vitamin A deficiency is the next most important criterion. Since these scars are expected to accumulate in the population, they should be detectable with smaller samples (unless a large proportion die). In general, the prevalence of XS paralleled, and thereby supported the prevalence found for X2/X3.

In all zones (including the component units of the sixth, composite zone) except East Java, rural prevalence rates exceeded the WHO criterion. Although the rural population of East Java is again spared, the urban slum (Surabaya) exceeded the WHO rate.

As with prevalence rates for X2/X3, none of the rates in rural zones were significantly different statistically from the average for rural Indonesia as a whole. Confidence limits for zonal rates are shown in Table 44. The mean prevalence of XS in the surveyed rural area of Indonesia as a whole was 13.1 $\pm$ 2.3 per 10,000 (P $\pm$ SE) and the 95% confidence limits were 8.5 - 17.7 per 10,000.

The least important clinical criterion is the presence of Bitot's spots, since they are not a measure of the magnitude of corneal involvement. Their popularity as a criterion stems from their greater frequency in xerophthalmic populations, and their presence is useful primarily when the size of the sample is insufficient to detect cases of corneal involvement (X2/X3 or XS). WHO's criterion for a significant problem (2 percent)was chosen, based on the assumption that this rate would be present under circumstances where the corneal criteria would also be met. As our study shows, this is not necessarily the case, at least in Indonesia. The prevalence of X1B in all zones was appreciable and roughly mirrored the extent of corneal involvement. But the fact

that corneal criteria were consistently encountered when the presence of Bitot's spots was greater than 0.5 percent pointed to the need for revising this criterion. In other cultures such as India, where unresponsive Bitot's spots seem more prone to accumulate in the population, the higher criterion might be valid, but we cannot be certain because the data from these countries is insufficient.

We encountered Bitot's spots in every rural and urban area studied (although not in every site), with the exception of the town of Padang.

The highest prevalence of Bitot's spots in rural zones was found in West Java, where the rate was significantly greater statistically than in Sulawesi, Kalimantan, and East Java ($p < .01$ for all). The prevalance of Bitot's spots in rural Central Java and Sumatra were significantly greater statistically than in Sulawesi ($p < .01$ and $p < .05$, respectively). The zonal rate was significantly higher statistically than the rate for rural Indonesia as a whole only in rural West Java ($p < .05$) and lower only in rural Sulawesi ($p < .01$). Among individual provinces, excluding those just discussed (West, East, and Central Java), rates of prevalence exceeding those for Indonesia as a whole occurred in Ambon, Aceh, and Lombok (2 percent, 2.4 percent, and 1.6 percent, respectively; $p < .05$ for each). Rates that were significantly lower than that of Indonesia as a whole, statistically speaking, occurred in South Sumatra ($p < .01$), South Sulawesi ($p < .01$), North Sulawesi ($p < .05$), and East Kalimantan ($p < .01$).

Confidence limits for zonal rates appear in Table 44. The mean prevalence of Bitot's spots (X1B) in rural Indonesia as a whole was 1.0 ± 0.070 per 100 ($p \pm SE$), and the 95% confidence limits were 0.86 - 1.14.

Summary of distribution of the problem. Except for Padang, evidence of xerophthalmia was present in the rural and urban populations of every province studied. Yet, taking all criteria as a whole, it is clear that the great bulk of xerophthalmia occurs in the rural population. Nonadjusted rates in rural areas were usually greater than in urban areas. (This was not always true, however, because urban rates were based on smaller samples. Thus the chance of finding corneal cases was reduced.) More important, 85 percent of the population lives in rural

areas.[22] In addition, urban rates apply only to slum dwellers; if adjusted to the total urban population, they would be considerably lower. Rural rates, on the other hand, are representative of the entire rural population in the areas studied. Nevertheless, the high level of disease among slum-dwelling urban children points to a significant problem in these populations, most strikingly in East Java, where the rural population seems less affected.

Although the rates are most valid for each zone as a whole, the disease seems to be especially prevalent in the following provinces, listed in descending order of prevalence (the prevalence of active corneal disease in Aceh is approximately 50 times greater than WHO's criterion; in Lombok, it is approximately 20 times greater):

Aceh	Bali
Lombok	South Sulawesi
Bengkulu	Ambon
West Sumatra	South Kalimantan
South Sumatra	West Kalimantan
West Java	North Sumatra
Central Java	Southeast Sulawesi
Central Kalimantan	

Magnitude of the Problem

The average (weighted) prevalence of active corneal disease (X2/X3) in the rural population covered in Study IV was 6.4 per 10,000 (see Tables 44 and 45). This represents 53 percent of the average prevalence during rounds 2 through 5 in Study I (see Table 39). Assuming that the conservative incidence of active corneal disease of 5.0 per 1,000 per year observed during rounds 2 through 5 in Study I applies to Study IV--in direct proportion to the ratio of the prevalence rates in the two studies--we can estimate the number of rural Indonesian children (ages 0 to 5) who develop active, significant xerophthalmic corneal involvement every year as follows:

$$\frac{\text{Prevalence of X2/X3 (Study IV)}}{\text{Prevalence of X2/X3 (Study I)}} \times \text{Annual incidence of X2/X3 (Study I)} = \text{Annual incidence in population at large}$$

or

$$\frac{6.4}{12.0} \times 5.0/1{,}000/\text{year} = 2.7/1{,}000/\text{year}$$

Annual incidence	X	Proportion of population under age 6	X	Proportion of population that is rural	X	Total population of Indonesia	=	No. of new corneal cases in rural areas each year
				or				
2.7/1,000	X	0.20	X	0.85	X	(138×10^6)	=	63,342

Thus, as a rough estimate, 60,000 additional Indonesian children each year develop significant degrees of new, active corneal xerophthalmia. And the number is even higher if the following children are added: (1) those living in urban areas,* (2) those age 6 and older, (3) those in the 4 percent of the population not covered by the survey, and (4) those excluded from the original calculation of incidence because they either died or underwent spontaneous cure between examination rounds.

As discussed earlier, we would expect at least 33 to 50 percent of the cases with clinically apparent corneal involvement to go blind--or an estimated 20,000 to 30,000 children every year. The overall (weighted) prevalence of corneal scarring (XS) almost certainly related to xerophthalmia in the rural, surveyed population of Indonesia was 1.31 (0.85 - 1.77) per 1,000 (see Table 44), or a total of 30,734 (19,942 - 41,526) children. The proportion of children with scars resulting in blindness or severe loss of vision in both eyes was 45 percent (21 out of 47), and in one eye, 43 percent (20 out of 47). Currently, at least 13,830 (30,734 x 0.45) noninstitutionalized Indonesian children are blind in both eyes from xerophthalmia (8,974 - 18,687).

At the rate of incidence observed, the minimal number of blinded children with corneal scarring that we would have expected to accumulate in the population was 60,000 (20,000 per year x 3 years). Since the actual number estimated is only 13,830, as many as 77 percent may have died. This estimate may be considerably higher than the true mortality rate for several reasons:

- The rate of incidence may not have been constant, but lower, during preceding years, although there is no evidence to suggest this was the case.

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*The survey indicated that slum dwellers, at least, are at risk of corneal disease.

- A significant proportion of the 104 cases with corneal scars that were not definitely attributable to xerophthalmia (XS groups 0-2) may in fact have been caused by the disease.
- Many blinded children may have been institutionalized and therefore were not at home to be counted. (We inquired about this possibility, but the paucity of such institutions severely limits the potential impact of this variable in any case.)
- A smaller proportion of active corneal cases may go blind than was estimated (although our estimate was based on four different samples, all of which yielded comparable results).

Although these considerations suggest the difficulty of arriving at a precise estimate, mortality was certainly high. A large proportion of these deaths were undoubtedly related to the severe systemic illness and generalized malnutrition that commonly accompany blinding forms of the disease. The fact that a child is blind may also influence survival.

Mortality need not be this high. Using a modified life table analysis (see Table 46), the overall mortality among children in Study II was only 12.6 percent over a 14-month period. This varied, however, from 3.8 percent for children without severe protein-energy malnutrition to 25.7 percent for children with severe protein-energy malnutrition: weight for height < 70 percent of standard, presence of edema, or serum level of albumin ≤ 2.5 gms/100 ml ($p < .01$). As expected, most deaths occurred during the first three months of observation.

D. Determinants and Associated Factors

Age

In Indonesia, xerophthalmia is essentially a disease of young children. As already noted, 72 percent of the individuals with vitamin A-responsive Bitot's spots examined in Study III and 96 percent with active corneal disease in Study II were under age 6 (see Tables 10 and 19). These were the only studies in which individuals of all ages were regularly examined. Although these percentages are based on clinic populations and therefore are not necessarily representative of the population at large, whatever bias is present should inflate rather than deflate the proportion of older individuals, who are more likely to notice and seek treatment for their disease.

The vast majority of active corneal cases in Study II occurred during the first 5 years of life. Almost half of all cases of limbus-to-limbus necrosis (files 7 and 8) occurred before age 2. As noted

earlier, these more severe forms tended to occur at an earlier age.

The age distribution of active corneal disease in the more representative sample of preschool-age children in Study IV was similar to that found in Study II (see Table 47). As expected, the age distribution for scarring is somewhat older. The age at which scarring was said to have occurred is in reasonably good agreement, considering the potential inaccuracy of historical data.

The age distribution of all 36,060 children examined (cards 40/41 match) is shown in Table 48. The overall distribution does not display the expected population pyramid, in part because children who were less than 2 months old were usually not examined. Other possible factors may be the effect of recently expanded family planning activities, annual variation in infant mortality, or errors in reporting. The distributions for males and females are similar. The magnitude of the potential error is relatively small and unlikely to affect the validity of the results, especially since there is no reason to suspect that any bias which may be present is different for normals and abnormals.

Age-specific rates of prevalence for Bitot's spots are shown in Table 49. Consistent with the results of Study III, rates were lowest during the first two years of life; we encountered only one case who was less than 1 year old. There is a statistically significant increase in the prevalence of Bitot's spots during each of the first three years of life ($p < .01$ for all); it subsequently rises slightly (and not to a statistically significant degree) to a plateau, and the pattern is the same for both sexes. The reasons for the consistent, although not statistically significant dip that occurs at age 4 are unclear.

The age distribution of Bitot's spots and active corneal disease are reasonably similar, except in older children, among whom Bitot's spots remain common while active corneal disease is rare. At least two factors may account for this difference. As already indicated, protein-energy malnutrition, which is generally more common among younger children, can potentiate and exacerbate the effects of vitamin A deficiency. It is also possible that the presence of Bitot's spots in older children does not necessarily represent active vitamin A deficiency, i.e., that some are sequelae of past disease. Although analysis of the results obtained from validation rounds 7 and 8 in Study I suggested that the

vast majority of cases were likely to be active, the prevalence of a history of night blindness among cases of Bitot's spots in Study IV dropped precipitously from 47.1 to 30.6 percent between the ages of 4 and 5 ($p < .05$). The proportion of cases in which Bitot's spots were observed both temporally and nasally (a more definite sign of active vitamin A deficiency than temporally alone, as shown in Study III) also declined between the ages 4 and 5--from 23 to 14 percent--although not to a statistically significant degree ($x^2 = 2.01$; df = 1).

Sex

In agreement with other reports, the findings in Study IV indicated that Bitot's spots were more prevalent among males than females: 1.25 versus 0.72 percent, respectively, a ratio of 1.7 to 1 ($x^2 = 25$, $p < .001$; see Table 49). This differential was present in every age group. The same was not true, however, for active corneal disease (X2/X3), which was more prevalent among females than males (7.4 versus 4.9 per 10,000, respectively, a difference that is not statistically significant). Although males suffered an excess of corneal scars (XS) attributable to xerophthalmia (16.2 versus 9.7 per 10,000), this too is not statistically significant and might be biased by a sex-specific differential in mortality. The difference in the prevalence of Bitot's spots and lack of a meaningful difference in the prevalence of corneal disease was also observed in Studies II and III. If these results are real, as they seem to be, rather than a chance variation, they can be explained in the same way as the differences in the age-specific prevalence of conjunctival and corneal disease. It is possible that although a greater proportion of males than females suffer from vitamin A deficiency, females deficient in vitamin A are more likely to be malnourished in general as well, and consequently the effect of their deficiency is more severe. Alternatively, for reasons poorly understood,* males may be more likely to maintain their Bitot's spots long after the underlying vitamin A deficiency has been corrected. Although the prevalence of a positive history of night blindness among males and females with Bitot's spots was similar, the prevalence of concomitant temporal and nasal lesions was higher among

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* Exposure or chronicity of the deficiency may play a role, as discussed earlier under conjunctival changes.

females than among males (27.6 versus 18.2 percent of cases of Bitot's spots, respectively; $p < .05$).

These findings are significant for the following reason: although they confirm the fact that males are more likely to have Bitot's spots, they suggest that males are not necessarily more likely to suffer xerophthalmic corneal destruction. Therefore, intervention programs must pay equal attention to both sexes.

Clustering

Although differences in the distribution of xerophthalmia between administrative areas with large populations have already been discussed, obvious differences exist in its distribution within these areas as well. It is impractical to conduct a study designed to identify each high-risk neighborhood, but it is important to recognize that the presence of a case of clinical disease suggests the neighborhood is at particularly high risk of containing additional children with clinical or subclinical xerophthalmia.

As already discussed, serum levels of vitamin A were obtained during round 1 of Study I from all abnormals; their clinically normal controls matched for age, sex, and neighborhood; and a 5 percent random subsample of the entire population (see Table 2). The levels among the abnormals were significantly lower than those among the controls, and in turn the levels among controls were significantly lower than those among the random sample (all differences were statistically significant; $p < .001$). This indicates that clinically normal children (matched controls) living in the immediate neighborhood of xerophthalmic children are significantly more likely to be deficient in vitamin A than are clinically normal children who live farther away (random sample). This is even more apparent when all abnormals and controls are removed from the random sample and the age distribution of the random sample is adjusted to that of abnormals and controls (not shown in Table 2). Given the high incidence and spontaneous cure rates encountered on subsequent clinical rounds, it seems reasonable to assume that (1) the dietary patterns, and thus the vitamin A status of families within any one neighborhood are similar and (2) slight changes in diet will cause today's xerophthalmic child to become normal by subsequent rounds and his almost equally vitamin A deficient normal neighbor to become xerophthalmic.

Clustering was also apparent in the distribution of clinical cases in Study IV. A statistical technique was devised to determine whether the occurrence of additional (secondary) cases in clusters already having one (primary) case was greater than would be expected if all cases had been randomly distributed. First, village clusters were separated into those with (index clusters) and without cases. Second, one case was subtracted from the number within each index cluster since index clusters were chosen on the basis of having a primary case. Third, the number of secondary cases that would be expected among the index clusters if secondary cases had been randomly distributed between index and nonindex clusters in proportion to the relative sizes of the populations "at risk" in these clusters was calculated. Fourth, the number of secondary cases expected in the index clusters was then compared with the number observed, and the normal deviate, corrected for continuity, was calculated.

If T = total number of cases, C = number of "index" villages, E = number of nonindex villages, Pc = study population in index villages, and Pe = study population in nonindex villages, then

$n = T-C$ = number of secondary cases (all having been observed, by definition, in index villages),

$p = (Pc - C)/(Pc + Pe - C)$ = proportion of population at risk of secondary cases that resides in index villages,

np = number of secondary cases expected in index villages, and

$$Zc = \frac{(n - np - 1/2)}{\sqrt{npq}} = \text{the normal deviate.}$$

Because of the larger number of cases, the effect of clustering on the distribution of cases of Bitot's spots could be most precisely defined. Statistically significant clustering at the village level was present in eight of the nine major regions (West Java, $p < .001$; East Java, $p < .01$; Central Java, $p < .001$; Sumatra, $p < .001$; Sulawesi, $p < .02$; Ambon,

$p < .001$; Kalimantan,* $p < .05$; and Lombok, $p < .001$). Only in Bali was the clustering not statistically significant--and the number of cases low. If Bali is combined with neighboring Lombok, clustering becomes statistically significant ($p < .001$).

The number of cases with active corneal disease was too low to calculate village-level clustering on a region-specific basis. Two regions in which there were no active cases (East Java and Ambon) are omitted from the analysis, which is designed to yield information on village-level clustering in regions where the disease occurs. (Had the two regions been included, the appearance of village-level clustering would have been heightened inappropriately.) Village-level clustering was present among the seven regions in which cases of active corneal disease occurred ($p < .001$).

A similar analysis for corneal scars (XS) was again statistically significant for clustering ($p < .001$). This time East Java, the only rural region without such cases, was omitted.

The clear-cut clustering of vitamin A deficiency and clinical xerophthalmia has potentially important implications for control programs. Rather than treat only individuals with recognized xerophthalmia, it might prove more efficient and effective if these programs focused on neighborhoods where a case of xerophthalmia is recognized.

Previous attempts to define the individual, familial, or environmental factors associated with the development of xerophthalmia have been hampered by the absence of suitable controls for comparison. For example, it is commonly reported (and observed) that a large proportion of xerophthalmia cases are preceded by diarrhea, the implication being that diarrhea precipitated or contributed to the disease. This may well be the case, but it is also possible that diarrhea is common in the community at large. If diarrhea is in fact a risk factor, it should be more common among individuals who have xerophthalmia than among those who do not.

In choosing controls, the more like the abnormals they are, the more precisely one is apt to identify the risk factors of greatest

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*East Kalimantan was excluded because no Bitot's spots were found there and including it would have increased the statistical significance even further.

importance within the milieu in which the abnormals live, especially those factors that are most amenable to intervention. For example, upper-class urban children who are exposed to protected water supplies and have many other advantages are far less likely to suffer from either diarrhea or xerophthalmia, which tells us little about the role of diarrhea in xerophthalmia. We are more interested in identifying the critical factors which account for the fact that among children who live under the same general conditions, some develop xerophthalmia while others do not. For these reasons, many of the analyses that follow rely on strict comparisons between abnormals and normal controls matched for age, sex, and neighborhood.

In Study II, which included the largest number of carefully examined corneal cases, we visited the neighborhoods of these cases and identified, recruited, and examined matched controls. Time constraints prevented us from visiting the neighborhoods of more than a sample of these cases, so the number of completely studied controls is limited. The strongest test, under these circumstances, was a paired comparison between each abnormal and his or her matched control, and this technique was frequently employed. Because the severity of xerophthalmia among cases for whom there were controls was identical to that of corneal cases as a whole (see Table 50), the results generally applied to the larger group. In Studies I and IV, matched controls were chosen for every case of Bitot's spots. Because controls were not always available, the number examined in Study IV was slightly lower than the number of abnormals (340 and 358, respectively). However, the age and sex distribution of abnormals and controls was identical, the number of missing controls was small (5 percent), and the size of both groups was so large that analyses were conducted on a nonpaired, group basis.

Four potential limitations to this analytical technique should be borne in mind:

- A condition that contributes to a disease may be so common in the community at large that it is impossible to detect a statistically singificant difference in its prevalence among abnormals and controls.
- In Study II, the sample of corneal cases for whom there were matched controls was limited. Thus none may have suffered a risk factor present in a significant proportion of corneal cases as a whole.

- As indicated earlier, children living in the same neighborhood as an abnormal were more likely to be vitamin A deficient than those living elsewhere. Since this applies to all controls, a significant but unknown proportion were likely to be subclinically deficient in vitamin A. Differences in the prevalence of factors believed to be associated with vitamin A deficiency may not be as great for abnormals versus controls as they would be if all controls had received adequate amounts of vitamin A. This probably accounts, at least in part, for the stepwise progression in difference occasionally observed between abnormals, matched controls, and randomly sampled children in Study IV.
- Even when a meaningful difference is detected, it need not have causal significance. For example, protein-energy malnutrition may be more common among abnormals because it increases the risk of xerophthalmia or simply because children who eat little food containing vitamin A also eat little of any other food. A confounding factor is that instead of contributing to the risk of xerophthalmia, protein-energy malnutrition or diarrhea may result from the underlying vitamin A deficiency that caused the xerophthalmia in the first place.

Although the number of cases of Bitot's spots (358) and matched controls (340) used to calculate prevalence rates in Study IV remained unchanged in the analysis of risk factors, the total base population was lower, for reasons already discussed. However, the age and sex distributions of the larger and smaller base populations were identical and the magnitude of the reduction was miniscule (36,060 to 35,274, a difference of 2 percent). In some analyses, especially the anthropometric ones, these totals were reduced slightly more by the absence of individuals for whom values were either lacking or obviously in error (out of range).

Among 60 potential matched controls recruited and studied in Study II, nine proved, on careful examination, to be clinically abnormal and were therefore excluded from the analyses. The remaining 51 were matched with 33 corneal cases, providing a maximum of 33 paired comparisons. In cases where more than one control was available for an abnormal, the average value of the controls was used in the paired comparison: for measurements such as serum levels of carotene, the mean was employed; for data on attributes (rates), fractional rates of positivity were calculated. Standard methods were used to calculate relative risk in case-control and prospective studies.[23]

Nutritional and Anthropometric Status

Vitamin A status. As discussed in detail earlier, levels of serum vitamin A and holo-RBP among corneal cases in Study II were uniformly

severely depressed. For completeness, it is worth noting that this was confirmed by the paired analysis of corneal cases and matched controls. The mean difference in serum levels of vitamin A was 10.2 ± 1.5 ug/dl ($\bar{u}$ ± SE, n = 16, $p < .001$), and in holo-RBP levels, it was 9.8 ± 1.6 ug/ml (n = 17, $p < .001$). The relative risk of corneal disease among individuals with serum levels of vitamin A above or below 15 ug/dl was 49 to 1, as determined by paired analysis.

Protein status. Serum levels of albumin and transferrin among cases of corneal disease in Study II were often, though not always depressed, as already discussed. The mean difference in albumin levels between corneal cases and matched controls, on paired analysis, was 0.84 ± 0.13 gms/100 ml (n = 32, $p < .001$). The mean difference in transferrin levels was 181 ± 22 mg/dl (n = 24, $p < .001$). The relative risk of corneal xerophthalmia among children with serum levels of albumin levels above and below 3.5 gms/100 ml was 49 to 1.

Edema. As already noted, 29 percent of corneal cases in Study II had clinical edema, and its prevalence increased with the severity of the disease. In paired comparisons, 21 percent of the corneal cases and none of the matched controls had edema (n = 33, $p < .01$).

Although not consistently assessed until late in Study IV, the prevalence of edema among preschool-age children in the population at large was extremely low: only a fraction of 1 percent. Clearly, the relative risk of corneal disease among children with pedal edema is extremely high.

Edema was less prevalent in milder forms of xerophthalmia. In Study III, only two of the 48 patients (4 percent) with vitamin A-responsive Bitot's spots had edema. This percentage is significantly lower than the one found among even mild cases of corneal involvement, X2 (19 percent; $p < .01$).

Although it is clear that special attention must be paid to children with edema, such efforts will include only one-third of the potential cases of corneal xerophthalmia and less than 10 percent of those with milder forms of disease.

Weight for height. Comparing a child's weight for height with that of well-nourished children is a practical means of determining the

adequacy of current nutritional status. The lower a child's weight for height, the more wasted he is.

Wasting was extremely common in the presence of active corneal disease. Among 159 patients with corneal disease in Study II whose weight for height was recorded, 46 percent were wasted to a moderate degree (weight for height $<$ 80 percent of standard), and 12 percent were severely wasted (weight for height $<$ 70 percent of standard). (See Table 24.) As discussed earlier, the severity of wasting increased with the severity of corneal involvement. In paired analysis with matched controls (n = 32), the matched control was more severely wasted than the abnormal in only three instances. The mean difference in percentage standard weight for height for these 32 comparisons was 15.0 percent $\pm$ 2.5 percent ($p < .001$). The relative risk of corneal disease among children with a weight for height that was less versus equal or greater than 80 percent of standard was 35 to 1.

Similar results were obtained in Study IV. Among the 22 cases of active corneal disease, 10 were at least moderately wasted, 5 severely so. As in Study II, the prevalence and severity of wasting increased with the severity of corneal changes. The prevalence and severity of wasting among corneal cases was greater than among cases of Bitot's spots (mean weight for height, 80 and 95 percent of standard, respectively; $p < .001$). This difference was not attributable to the age structure of the two groups since at every age but 1 year, the mean weight for height among cases of X1B was greater than 90 percent of standard, and in that single exception it was 86 percent (see Table 51).

Consequently, there is little doubt that active corneal disease, no matter how severe, is associated with acute, active wasting. A cut-off at less than 80 percent of standard would include approximately 50 percent of all corneal cases but only 10 percent of all children (see Table 52).

Although active corneal disease was associated with wasting, the presence of Bitot's spots (X1B) was not. The distribution of mean weight for height among children with Bitot's spots was identical to that of matched controls and all other normals (see Tables 51 and 52). Weight for height is therefore useless as an index of active noncorneal xerophthalmia or mild vitamin A deficiency.

Height for age. Unlike weight for height, height for age reflects long-term growth, which is affected by restrictions in both calories and protein, severe systemic illnesses, and other insults. Diminished height for age is called stunting.

In Study II, children with active corneal disease were shorter than their paired matched controls (difference = 2.7 percent of expected height for age, $n = 27$; $p < .05$). Surprisingly, the degree of difference was inversely proportional to the severity of corneal involvement ($r = 0.9995$, $p < .001$ see Table 53). These results may have reflected differences in the age structure of the respective groups: because severe corneal cases tended to be younger, there was less time for a difference to appear.

Because the survey in Study IV was conducted relatively quickly, age in months, which was required to use published height-for-age standards, was less certain. Therefore, a different analysis was used. Rather than compute height for age as a percentage of standard, we computed the mean height for age in years among the various groups and used it for comparisons. As in Study II, children with active corneal disease were clearly stunted: at every age, they were shorter than were children with Bitot's spots, their matched controls, or the rest of the population ($p < .01$; see Table 54).

In other words, the results of Studies II and IV provide strong evidence that children with active corneal disease are not only wasted but also stunted. Although children with Bitot's spots were not more wasted than the remainder of the study population, they were more stunted: on the average by 2.6 cm when compared with their matched controls ($p < .01$; see Table 54). There was no difference between the height of matched controls and the height of the other children examined.

The association between active xerophthalmia and anthropometric status can be summarized as follows: active corneal disease is associated with both stunting and (active) wasting, while milder xerophthalmia (Bitot's spots) is associated only with stunting. Thus wasting appears to be a critical difference between mild and severe xerophthalmia, and children with wasting are at especially high risk of corneal disease. The question that remains unanswered is whether wasting (and all it represents, e.g., increased protein deficiency, poor diet) contributes to the

manifestations of xerophthalmia (as data presented earlier suggests), whether wasting merely indicates that children whose intake of vitamin A is especially low are likely to have an especially low intake of other nutrients as well, or whether severe vitamin A deficiency contributes directly to poor nutritional status. Milder, though clinically significant vitamin A deficiency (as in Bitot's spots) does not seem to influence acute nutritional status.

Other deficiencies. Clinical manifestations of other forms of nutritional deficiency were not sought in Study IV. As indicated earlier, stomatitis alone was common among the active corneal cases in Study II, and at a rather uniform rate of 20 percent in all categories of disease. In paired analyses, it was present in 5 out of 32 cases (16 percent) and one of the controls (3 percent), a difference that was not statistically significant.

Nonocular Illness (Excluding Measles)

Diarrhea. Among the 156 cases of active corneal disease (X2/X3) in Study II with completed pediatric examinations (96 percent of the total), 11 had gastroenteritis (7 percent). There were no clinically meaningful or statistically significant differences by severity of corneal disease. Among the 33 cases for whom there were matched controls, the rate was almost twice as high as among their matched controls (12 versus 5 percent), a difference that was not statistically significant.

Although active, clinically significant gastroenteritis may not have been significantly more common statistically among abnormals than controls at the time of examination, a history of diarrhea in the recent past was. Seventy-two percent of all 162 cases had a history of diarrhea (four or more loose stools a day) at some point during the previous month--a rate that was essentially independent of the severity of corneal disease. The rate among the 33 cases in the paired comparison was 79 percent and among their matched controls, 23 percent ($p < .001$). The relative risk of corneal disease among individuals with and without a history of diarrhea during the previous month was 13 to 1. A majority of the diarrheal episodes were said to have occurred within the previous week. Again, there was no meaningful difference in the history of diarrhea by degree of corneal severity.

The same phenomenon was observed in Study IV. The prevalence of a positive history of diarrhea within the previous two months was significantly more common among cases of Bitot's spots than among their matched controls (61 versus 52 percent; $p < .01$). The greatest difference was for the previous week (10.1 versus 3.5 percent; $p < .001$). Age-specific rates indicate that this difference in rates of diarrhea during the previous week was present at ages 2 through 5 (see Table 55), and the average relative risk of Bitot's spots among children with and without a positive history in this age range was 4.5 to 1. Rates of diarrhea among the remaining children studied and the matched controls were identical. There was no meaningful, consistent difference between males and females in any category.

If the association between both mild (X1) and severe (X2/X3) xerophthalmia and a recent history of diarrhea is, in fact, causal, there are several possible explanations. Diarrhea may increase the risk of xerophthalmia, or xerophthalmia (and its accompanying vitamin A deficiency) may increase the risk of diarrhea. On the other hand, the presence of ocular disease may affect the parent's response to the question--a problem with all historical data. The fact that the association with diarrhea is greatest for the week immediately preceding the examination, when the vast majority of Bitot's spots surely were already present, suggests that either xerophthalmia led to the diarrhea or, as one might expect, the reliability of historical data declines the longer the duration between the event and its recall. As mentioned many times, simply because two conditions are associated does not necessarily mean that they are causal in either direction. They may be linked through some common third variable.

Worms. Between one-fourth and one-third of normals and abnormals (regardless of the xerophthalmia's severity) in Studies II and III had a history of passing worms during the preceding month. Roughly 50 percent of the abnormals and matched controls tested were excreting Ascaris eggs, and one-third of this group was passing Trichuris as well.

Although xerophthalmia was not associated with worms in Studies II and III, it was in Study IV: 22 percent of the cases with Bitot's spots, 14 percent of the matched controls, and 9 percent of the remainder of the sample claimed to have passed worms during the previous month, rates

that were statistically significant but different from one another ($p < .01$). Although a history of worms and the presence of Bitot's spots seemed to be associated in this larger, more respresentative sample, the relative risk of Bitot's spots among individuals with and without a history of worms is only 1.7 to 1, with some variation by age (see Table 56) but not by sex.

Anorexia or vomiting. Twenty to 25 percent of the children in Studies II, III, and IV, regardless of clinical classification (including nonxerophthalmic) were said to have had at least one episode of anorexia or vomiting during the previous month. The duration between examination and most recent episode was also similar.

Respiratory tract disease. Respiratory tract disease (fever plus cough or rales) was the commonest condition accompanying corneal disease in Study II. Its prevalence was directly related to the severity of corneal involvement ($p < .01$; see Table 57). By paired comparison, respiratory tract disease was clinically and significantly more common statistically among cases of X3B than among their matched controls (7 out of 11 versus 1 out of 11; $p < .01$). Among cases with less severe corneal disease (X2, X3A), the prevalence of respiratory tract disease was identical with that of their matched controls, which suggested something extremely unusual among cases of X3B. It was unclear whether the severity of xerophthalmia and the accompanying malnutrition led to the respiratory tract disease among cases of X3B or whether the combined effects of generalized or protein malnutrition and respiratory tract disease on the metabolism of vitamin A resulted in xerophthalmia being manifested in its more severe form.

Confirming the pattern noted above, a history of a cough during the previous month was significantly more common among cases of X3B than X3A or X2 (27 percent versus 16 and 17 percent, respectively; $p < .01$). In paired comparisons, the prevalence of coughs among the 33 corneal cases was significantly higher than among their matched controls (30 versus 9 percent; $p < .05$). Although severity-specific differences were highest for cases of stromal involvement (X3A and X3B), none were statistically significant by themselves. Data were not collected on coughs in Study IV.

Severity of clinical (nonocular) status. The pediatrician

classified all children by the severity of their general (nonocular) clinical status as normal, minimally ill, moderately ill (requiring bed rest), or severely ill (life-threatening). All 50 children in Study III (X1) and 141 of the 162 children (87 percent) in Study II (X2/X3) were classified (see Table 58). In general, the severity of nonocular disease paralleled the severity of the ocular one. Even the difference between noncorneal (X1) and the mildest corneal disease (X2) was statistically significant ($p < .01$). More than half of all corneal cases were regarded as at least moderately ill, half of them severely so. Half of all cases of X3B were severely ill.

In the paired comparison in Study II, 58 percent of the abnormals and none of the matched controls were moderately or severely ill. Twenty-seven percent of the matched controls were minimally ill.

Although the absence in this small sample of any matched controls that were moderately or severely ill precludes formal calculation of relative risk, it is clear that the risk had to be extremely high and that the more severe the corneal disease, the higher it was. For example, had one of the matched controls been moderately or severely ill, the relative risk of corneal disease among those that were moderately or severely ill as opposed to those that were not would have been 43 to 1. Had two matched controls been moderately to severely ill, the realtive risk would have been 21 to 1.

Although Studies II and III were clinic-based, we have already seen that their results are generally confirmed by those of Study IV. Assuming that these results are broadly applicable as well, it is clear that a majority of children with severe corneal disease, but only a small proportion of the population at large, is severely ill. Treatment of all severely ill children will therefore have a high cost-benefit ratio. But because the interval between the onset of severe general disease and corneal destruction may be short, it may be difficult to identify and treat a substantial proportion of these cases before they go blind.

Measles

The role of measles in pediatric blindness is discussed separately for several reasons. First, in other cultures (most notably, Africa),

measles rather than xerophthalmia is claimed to be the most important cause of pediatric blindness by far, contrary to the experience in Asia in general and in Indonesia in particular. Second, despite these expectations, measles appears to account for a significant proportion of cases of pediatric blindness in Indonesia, especially of the severest, blinding type. Third, vitamin A deficiency seems to be the mechanism through which measles has its affect. And fourth, advances in immunization against measles suggest that measles prophylaxis may be an effective means of significantly reducing the problem of blinding xerophthalmia in Indonesia.

Among the 162 cases of active corneal disease enrolled in Study II, 6 (or 4 percent) had evidence of active measles. In all six cases, the disease was said to have appeared during the preceding one to three weeks. All were cases of corneal necrosis (X3B), the prevalence of measles in files 6 and 8 (11.3 percent; five cases in file 6, one in file 8) being significantly higher statistically than among cases of the milder forms of disease ($p < .001$). Every one of these six children had extremely low serum levels of vitamin A, holo-RBP, or both.

Among five cases of active or recent measles excluded from Study II, two contained atypical ulcers bilaterally. Although the diagnosis of xerophthalmia was therefore clinically uncertain, levels of vitamin A in both were severely depressed (7 ug and 5 ug/100 ml). In one, night blindness preceded the onset of measles. The three remaining measles-associated cases were examined later, after corneal healing had begun, and all three suffered stromal involvement (potentially files 4-6), which was binocular in two. Two of these children had already received vitamin A therapy for their ocular changes, and one of the two had a long history of night blindness. As far as we could determine, the third had not received vitamin A therapy: his holo-RBP was 0 mg/100 ml. The other two had received large amounts of oil-miscible vitamin A parenterally (100,000-400,000 IU); yet their serum levels of vitamin A were still low: 13 and 16 ug/100 ml. These five cases represented a disproportionate share of corneal cases excluded from Study II. Including them, as well as other cases excluded for similar reasons, would have raised the prevalence of measles among active corneal cases in Study II considerably.

Although measles was more common among abnormals (n = 2) than matched controls (n = 0) in the paired analyses, the numbers were too small to be statistically significant.

A history of recent measles was more common than the presence of clinically active disease. Among the 162 cases formally enrolled in Study II, nine had a history of measles during the previous month, and an additional two, during the previous two months. These 11 cases represented 17 percent of all cases of X3B (files 6-8) and 7 percent of all cases as a whole--a difference that was statistically significant ($p < .01$; see Table 59). None of the 50 cases of Bitot's spots in Study III had a history of recent measles.

This same pattern of measles involvement was observed to an even more exaggerated degree in Study IV. Bitot's spots were not associated with any meaningful increase in the age-specific prevalence of measles (by history) during the preceding month: the rate among abnormals and matched controls averaged 5.9 and 4.8 percent, respectively (see Table 60). In contrast, 8 out of 22 cases (36%) of active corneal disease claimed to have had measles during the preceding month, a rate many times that of the rest of the population ($p < .001$). The relative risk of active corneal disease among those with and without a recent history of measles was 11 to 1. Even more striking, the parents of 64 percent of all children with active corneal cases (79 percent of cases with stromal lesions, X3A or X3B) claimed that measles had preceded the onset of corneal disease by one to four weeks.

Why measles was more common among cases of active corneal disease in Study IV than Study II is uncertain. It is possible that Study IV simply reflected the pattern of disease in the community at large more accurately--as indeed it was meant to. Alternatively, a large proportion of the areas examined in Study IV may have undergone a measles epidemic at the time, although the low prevalence of measles among noncorneal cases suggests that this was unlikely.

Among the 47 cases of xerophthalmic corneal scarring (XS) encountered in Study IV, 24 (or 51 percent) had a history of measles that preceded the onset of their corneal disease by one to four weeks. Among cases of bilateral blindness or severe visual handicap, the rate was still higher: 13 out of 21, or 62 percent. These rates are remarkably consistent with

those for active corneal disease in the same study (IV). As expected, a history of measles during the month preceding examination was far less common among cases of XS than among cases of X2/X3 (one out of 47, or 2 percent), a finding which is consistent with the findings obtained in the other groups in Study IV that were free of active corneal disease.

On the basis of these findings, it seems clear that (1) measles is associated with a large proportion of the corneal destruction and blindness that occurs in Indonesian children and (2) children with active corneal destruction associated with measles have little or no circulating vitamin A (this was the case in all instances studied). Regardless of the exact mechanism(s) by which measles causes corneal destruction in the presence of vitamin A deficiency, it seems certain that prevention of measles per se would have a significant impact on the problem of blinding xerophthalmia in Indonesia.

Breast Feeding

Among children of all ages in Study IV, those with Bitot's spots were less likely to breast feed than were their matched controls ($p < .001$; see Table 61). Among 1 year olds--the youngest age for which reasonable numbers of cases are available--the rates were 24 and 71 percent, respectively. Since the contribution of breast milk to children's diets diminishes with age, it is not surprising that the relative risk of Bitot's spots among children who do not breast feed, compared with those who do, diminishes as well: from 8:1 at age 1 to 2:1 at age 2 to 1:1 at age 3 (based on abnormals and matched controls).

There were no meaningful sex-specific differences in the prevalence of breast feeding or in the age at which weaning began.

The lack of breast feeding and presence of Bitot's spots were not only related but likely to be causal. An alternative explanation--that children who were sickly in general developed xerophthalmia and stopped breast feeding because of their illness--seems unlikely. The reasons the mothers gave for discontinuing breast feeding were the same in all three clinical groups: the vast majority either said they felt it was no longer necessary or said they had become pregnant (53 and 35 percent, respectively; see Table 62).

The attributable risk--the maximum proportion of cases of Bitot's

spots that might have been related to lack of breast feeding among 1 year olds--was 68 percent. Difficulties inherent in altering other aspects of infants' diets and their low exposure to potentially fortifiable foods (which will be discussed later) suggest that changes in breast-feeding practices must be an important goal of any program for the prevention of xerophthalmia. Although no abnormals were less than 1 year old, it is reasonable to suspect that differences in breast feeding between future abnormals and normals existed, as they did at every other age, and that these differences may have contributed to the development of xerophthalmia in 1 year olds and probably older children as well.

Diet

Dietary comparisons were available for cases of active corneal disease and matched controls in Study II and for cases of Bitot's spots and randomly sampled normals in Study IV. Although programming problems precluded comparisons with matched controls, there were no significant differences between matched controls and the remainder of the normal study population based on any variables already examined or on family consumption patterns, which will be discussed later.

Active corneal disease: Study II. To gain some feeling for the relative contribution of various foods to the diet and the differences in consumption patterns by classes of foods (individual items combined), frequency of consumption was scored as follows: 1 = more than once a day, 2 = once a day, 3 = at least once a week, 4 = at least once a month, 5 = less than once a month, 6 = never. These scores represented progressively less frequent, mutually exclusive categories. Liver, eggs, fresh fish, and meat all contain vitamin A to varying degrees. Green leafy vegetables (glv), carrots, mangos and papaya contain beta carotene (provitamin A). Soy (tempe or tahu) does not contain vitamin A or beta carotene.

In Study II, matched controls consumed more of every food listed than did corneal cases (see Table 63).

Differences in consumption of soy were insignificant. In part this may reflect the absence of vitamin A/beta carotene, precluding any causal relationship with xerophthalmia, and in part that soy was by far the most frequently consumed item in both groups (77 percent of

abnormals and 90 percent of matched controls ate it at least once a week).

Matched controls as a whole clearly ate more foods containing vitamin A and beta carotene than did children with corneal disease ($p < .001$). Significantly, the greater proportion of their advantage was in the consumption of sources of beta carotene ($p < .01$).

Of the three potential sources of beta carotene listed, the smallest and statistically insignificant difference between abnormals and matched controls was for mango and papaya; the largest differences were for the less expensive sources of beta carotene: glv and carrots ($p < .02$ and $p < .01$, respectively). It is interesting to note that a large proportion of abnormals (33 percent) consumed glv at least once a week, but this was not often enough, the quantity consumed at each serving was too small, or other factors interfered with utilization of beta carotene. The relative risk of active corneal disease decreased as frequency of consumption increased. For example, when abnormals who ate no glv were compared with normals who ate them more than once a month but less than once a week, the difference in risk was 3.7 to 1. The difference in risk increased to 7.3 to 1, however, when the comparison group ate glv more than once a week. The existence of this relationship increases the likelihood that the association is causal: i.e., reduced consumption of glv results in an increased risk of xerophthalmia.

The single greatest statistically significant difference in food consumption by abnormals and matched controls was for carrots. But far fewer children in both groups ate carrots than glv. As with glv, the relative risk of corneal disease among those who did not eat carrots increased in direct proportion to the frequency of consumption among those who did eat them.

Paired comparison of serum levels of carotene among abnormals and their matched controls confirms the dietary data: the level among controls was 11.6 ± 1.9 ug/100 ml higher than among the paired children with active corneal disease ($n = 15$, $p < .001$).

Among the four foods containing vitamin A differences in frequency of consumption by abnormals and controls was lowest for liver, an insignificant $\bar{u} = +.032$. In part this lack of association may reflect the fact that liver was rarely consumed (only 3 percent of abnormal and control children ate liver at least once a week). The difference in

consumption of meat, a relatively poor source of vitamin A, was greater but still not statistically significant. Both eggs and fish were eaten more frequently by controls ($p < .05$ for each). Although both were eaten by a large proportion of abnormals, few ate them often: only 7 percent of abnormals were said to consume eggs and only 17 percent, fresh fish, as often as once a week.

As with glv and carrots, the relative risk of corneal disease among children who did not eat eggs was directly related to frequency of consumption in the comparison group--2.3 to 1 when the comparison group consumed eggs at least once a month but less than once a week; 8 to 1 when the comparison group ate them at least once a week.

Unlike eggs, the relative risk of corneal disease among children who did not eat fish (a relatively poor source of vitamin A, unless the liver is eaten) did not vary in any consistent or meaningful way with the frequency of consumption in the comparison group. This suggests that the association between active corneal disease and infrequent consumption of fish is more likely to be indirect than is the association between active disease and infrequent consumption of glv, carrots, or eggs.

In summary, differences in dietary intake of foods rich in vitamin and provitamin A probably accounts for much of the active corneal xerophthalmia encountered in Study II. The greatest (and most likely causally related) differences concerned intake of glv and carrots, which are relatively inexpensive, readily available sources of beta carotene. These data strongly support the notion that increased intake of glv should have a significant impact on the problem of blinding xerophthalmia. Because almost two-thirds of abnormals in the paired comparison already consumed glv at least once a month, much could probably be accomplished by increasing the frequency of consumption of glv in this group or the quantity consumed per feeding. The same applies to the consumption of eggs. Although more expensive than glv, they were, somewhat surprisingly, consumed at least once a month by almost half the abnormals.

Bitot's spots: Study IV. Except for fresh fish, there was no consistent or meaningful sex-specific difference in patterns of food consumption. Therefore, males and females are combined in all but one of the following analyses.

Normals consumed glv more frequently than abnormals at every age ($p < .01$ for all but 1 year olds, for whom the difference was not statistically significant; there were too few cases, n = 1, to permit analysis below age 1). (See Table 64.) Surprisingly, a sizable proportion of abnormals claimed to consume glv at least once a week. The reasons why they might have developed xerophthalmia, aside from errors in reporting, were reviewed during the discussion about this phenomenon among cases of active corneal disease. Interestingly, the Chi-square value for the difference in consumption by abnormals and normals was highest for ages 3 and 5, the ages at which the prevalence of Bitot's spots was also highest.

Use of mango and papaya, the other major sources of beta carotene investigated, is shown in Table 65. As with glv, normals consumed them more frequently at every age; unlike the situation with glv, the greatest differences, and the only ones that were statistically significant, occurred early in life, ages 1 and 2 ($p < .02$ and $p < .03$, respectively). Although more abnormals and controls ate glv regularly (at least once a week) than fruit at older ages, more ate fruit regularly during the earlier years. This indicates that although glv may be more widely available, it is introduced into the child's diet later in life for reasons discussed later. This undoubtedly accounts for the greater association (importance) of patterns of fruit consumption than of glv consumption with xerophthalmia during the second year of life (age 1).

Although blood samples were not obtained in Study IV, data from Study I, round 1, confirmed that the same association between serum levels of carotene and cases of xeropthalmia observed with active corneal disease (Study II) was also true for Bitot's spots. In a paired analysis of cases of Bitot's spots and matched controls, serum levels of carotene were 8.5 ± 1.2 ug/100 ml higher among the controls ($n = 110$; $p < .001$).

It has already been suggested that in some instances, outside factors may affect proper utilization of ingested carotene. One factor may be adequacy of dietary lipids since lipids are required for absorption and conversion of carotene to vitamin A. Although it is impossible to say whether inadequate intake of dietary oils was limiting utilization of carotene to a clinically significant degree, edible oils were consumed

less frequently by abnormals than normals at every age. Interestingly, the greatest differences occurred at ages 3 and 5 ($p < .04$ and $p < .06$, respectively; see Table 66), the ages at which Bitot's spots were most prevalent.

Suggestions that consumption of both oils and glv (preferably together) should be encouraged seem reasonable and supported by available data.

Of the three foods containing vitamin A--eggs, fresh fish, and meat--differences in meat consumption were the least significant. Although meat was eaten regularly (at least once a week) by a larger proportion of normals than abnormals at every age, the difference was statistically significant only for 5 year olds (see Table 67). In addition, the proportion of normals who consumed meat regularly was less than 25 percent.

Fresh fish was consumed regularly by twice as many children as was meat--the only instance in which a sex-specific difference occurred (see Table 68). Among males, normals consumed meat more frequently than did abnormals at every age, but again the difference was statistically significant only among 5-year-olds ($p < .005$). Among females there was no consistent, meaningful, or statistically significant difference in consumption of fish between normals and abnormals.

At every age, a larger proportion of normal children than those with Bitot's spots consumed eggs regularly (see Table 69). Although the magnitude of the difference was similar in all age groups, it was statistically significant only for years 2 through 5, not year 1 (probably because of the smaller number of cases involved). As in Study II, a majority of children claimed to consume eggs at least once a month.

In summary, results of dietary analyses in Studies II and IV were remarkably consistent: major differences existed in the consumption of foods containing vitamin and provitamin A between normal children and those with mild (X1) and severe (X2/X3) xerophthalmia. The greater part of this difference was in the consumption of inexpensive, readily available sources of beta carotene (especially glv) and not in the consumption of relatively expensive sources of preformed vitamin A. Since the vast majority of children already eat some glv, especially those ages 2 to 5, the task of increasing their intake may prove to be less formidable than was originally supposed.

Few very young children (age 0-1) consume glv, and differences in its consumption between abnormals and controls does not account for the presence of xerophthalmia. It appears that differences in fruit consumption and breast feeding practices are largely responsible for xerophthalmia in this age group. Influencing these two patterns might be an easier and more effective method of preventing xerophthalmia in 0 to 1 year olds than would attempts to increase the consumption of glv.

Intake of edible oils, essential for optimal absorption and use of sources of vitamin and provitamin A, was lower among abnormals. This may be clinically significant, especially among children who were already consuming low to borderline amounts of foods containing vitamin or provitamin A. Consequently, increased intake of edible oils as well as glv and fruits should probably be encouraged.

Demographic and Socioeconomic Factors

A large variety of demographic and socioeconomic factors were investigated in Study IV. Three groups were available for comparisons: children with Bitot's spots (358), their matched controls (340), and "normals" (the remainder: all normals minus the 340 matched controls) (34, 576). Since normals were not matched by neighborhood with the two other groups, some differences between normals and the others may reflect variations between populations of affected and unaffected communities. As it turned out, in only one of 12 variables analyzed was there a significant difference between normals and matched controls, and that involved the composition of the walls of the house, the one variable most likely to vary by village or region. In that instance, as well as additional ones in which small and statistically insignificant differences were present between matched controls and normals, the matched controls were always the more disadvantaged.

Six variables can be viewed as primarily economic in nature, although many obviously have social and behavioral implications as well: (1) composition of the walls of the house, (2) source of lighting, (3) source of drinking water, (4) principal bathing facility, (5) principal occupation of head of household, and (6) frequency of the family's meat consumption. There was a statistically significant difference between abnormals (X1B) and matched controls in three: principal bathing

facility, principal occupation of head of household, and frequency of the family's consumption of meat. The proportion of families using poor bathing facilities was greater among the abnormal group ($p < .05$), but the differences in overall distributions were not statistically significant according to the X^2 test. The proportion of low incomes was also greater among families of abnormals ($p < .001$; difference in overall distribution by X^2, $p < .002$; see Table 70). Consumption of meat tended to be less frequent among families of abnormals (difference in overall distributions by X^2, $p < .05$). Abnormals were also worse off for the other three variables but not to a statistically significant degree.

Six variables could be regarded as primarily social or demographic in nature: (1) number of people living in the house, (2) number of children under age 6 in the house, (3) educational level of head of household, (4) person primarily responsible for caring for the child, (5) number of live births to the child's mother, and (6) death rate among those live births. Statistically significant differences between abnormals and matched controls were present for three variables: number of people living in the house, educational level of head of household, and mortality of live births to the child's mother. The proportion of families with five or more persons living in the house was higher among the abnormal group ($p < .02$), but the difference in the overall distribution was not (by X^2). In terms of educational level of the head of the household, the abnormals were also worse off (difference in overall distribution by X^2, $p < .05$). The mortality rate among live births to mothers of abnormals was 16.2 percent; matched controls, 13.2 percent; and normals, 11.8 percent ($p < .001$ for linear trend). The mortality rate among siblings of abnormals was significantly higher statistically than among siblings of matched controls or normals ($p < .05$ and $p < .001$, respectively). The difference in mortality between siblings of matched controls and normals was not statistically significant.

Among the three variables for which there were no statistically significant differences, abnormals differed from matched controls in one: they were more likely to be born to mothers who had given birth to large numbers of children. Abnormals did not differ from matched controls or normals by the number of children under age 6 who lived in the household or by the person primarily responsible for their care (in all instances,

mothers accounted for 95 percent of the total).

These relationships will be explored in greater depth using multivariate analyses. In the end, however, one would be left with the same conclusion, that lower income families are at higher risk of having children with xerophthalmia and that the socio-economic and demographic factors do not cause xerophthalmia, but are associated with the nutritional factors that are the underlying causes of xerophthalmia.

In summary, although abnormals were more likely to be members of socioeconomically depressed families, the differences were slight in all instances and provided no useful or practical means of identifying, reaching, or influencing the population at risk of xerophthalmia.

E. Screening

Screening is a technique used to identify individuals already having a particular condition (e.g., vitamin A deficiency), or likely to develop one (e.g., xerophthalmic corneal destruction). We have already alluded to situations in which this could be usefully applied: children with severe illness or protein-energy malnutrition should all receive systemic vitamin A and general supportive care since they are at particularly high risk of corneal disease.

A simple field test for vitamin A deficiency would be extremely useful since it would identify children in need of attention long before they go blind. Although an ideal test does not yet exist, at least one simple technique--inquiring whether a child is night blind--may prove useful for identifying at least a portion of children who need treatment and for increasing the yield of xerophthalmia cases in prevalence surveys.

History of Night Blindness

Data collected in round 1 of Study 1 suggests that a properly elicited history of night blindness can be just as specific and twice as sensitive a marker of vitamin A deficiency as the presence of Bitot's spots. Mean serum levels of vitamin A in children with a history of night blindness (with or without Bitot's spots) and Bitot's spots (with or without a history of night blindness) were similar, while the number of children with a history of night blindness was twice the number that had Bitot's spots (see Table 1). Although obtaining histories of night blindness

enabled us to identify twice as many children as did the presence of Bitot's spots, the fact that only 61 percent of all cases of Bitot's spots had a history of night blindness suggests that the sensitivity of this screening method is less than ideal. For comparison, recall that in Study III at least 85 percent of children with Bitot's spots which responded to vitamin A proved, an objective assessment, to be night blind.

Nevertheless, the results are extremely encouraging and suggest that asking whether a child is night blind--a simple task for even non-medical personnel such as village health workers, teachers, and siblings--one could identify a large proportion of children requiring vitamin A treatment and prophylaxis. As we have already seen, vitamin A therapy cured night blindness in the vast majority of children studied in validation rounds 7 and 8 in Study I.

Data from Study II suggests that treating all cases with a history of night blindness may even reduce the incidence of severe corneal disease. Among the 162 cases of corneal disease identified in Study II, the presence or absence of a history of night blindness was recorded for 147 (91 percent of the total). Among these, a positive history of night blindness was present in 83 (or 57 percent), and the rate among those with night blindness was higher than those with stromal involvement (75 percent with X2, files 1-3; 45 percent with localized stromal lesions, files 4-6; and 56 percent with complete loss of at least one cornea, files 7-8). Duration of night blindness was known for 99 percent of the 147 (145). Because the parents of between one-third and one-half of all children with corneal disease, including the most severe, claimed that the children had been night blind for at least three weeks, there seemed to be ample opportunities for intervention between the onset of night blindness and onset of active corneal disease.

The results of Study I are most analogous to those we might expect from regular, ongoing, village-based screening programs, where local workers, known and trusted by the community and familiar with the language and culture, seek children in need of therapy. In contrast, the results of the countrywide survey (Study IV), which was conducted by three teams working rapidly in areas where they were often unfamiliar

with the language and culture, are probably a better index of this technique's value in establishing the prevalence of xerophthalmia and vitamin A deficiency in a population.

Since blood samples were not collected and night vision was not assessed objectively, the validity of the results in Study IV can only be determined indirectly. The specificity appears to have been extremely high. Children with other evidence of vitamin A deficiency (e.g., Bitot's spots) were 178 times as likely to have a history of night blindness as those who did not. In Study I, the ratio had been 14 to 1. In an alternative comparison, 65 percent of all children in Study IV who claimed to be night blind had Bitot's spots, versus 31 percent in Study I (see Table 2). This suggests not only that the specificity of screening in Study IV was high but that the sensitivity of screening among those without Bitot's spots was extremely low.

Since preschool children with Bitot's spots were likely to be vitamin A deficient, the frequency with which they reported night blindness was probably the surest criterion by which to compare the sensitivity of screening for nightblindness in the two studies: 50 percent of the children with Bitot's spots in Study IV (178 out of 358) and 61 percent in Study I claimed to be night blind. As shown in Table 71, however, the prevalence of night blindness reported among cases of Bitot's spots in Study IV varied from a high of 76 percent in Central Java to a low of 10 to 12 percent in Ambon and East Java. The rate in West Java was identical to that recorded in Study I, which indicated that what led to difference in rates of night blindness recorded in Studies I and IV was not so much the differences among teams--all of which were composed of individuals from West Java--but the differences in the cultures they surveyed.

It is unclear whether the culture-dependent variation reflects differences among the various cultures in recognition of night blindness or reflects difficulties the teams encountered in identifying the locally appropriate word or phrase to describe the condition. Whatever the reason, inquiring about a history of night blindness resulted in relatively few additional cases of vitamin A deficiency when compared with the number already identified by the presence of Bitot's spots.

In Study IV the ratio of children lacking Bitot's spots but having a history of night blindness to those with Bitot's spots was 97 to 358 (0.27). In contrast, the ratio in Study I was 174 to 130 (1.34). In other words, inquiring about the presence of night blindness increased the yield of clinical cases of vitamin A deficiency by only 27 percent.

In summary, historical screening for night blindness should prove, at least in high risk areas, to be an important and useful technique by which local workers can identify a significant proportion of children who require vitamin A therapy and long-term prophylaxis. Its value in prevalence surveys, however, is likely to be somewhat limited, although this may depend to a large extent on the team's familiarity with the local culture.

Vital Staining

Application of vital stains such as Rose Bengal and Lissamine Green to the eye has been advocated as a useful means of distinguishing responsive from unresponsive Bitot's spots and detecting preclinical xerophthalmia as well as a simple screening tool for use by inexperienced field workers.[7] Unfortunately, our own investigations, primarily in Studies II and III, do not bear out these claims. For one thing, attempts to reproduce and standardize the results obtained by this method were less successful than by direct clinical categorization of the lesion itself. Although specificity was not too unreasonable--only 12 percent of normal controls "definitely" stained in one or both eyes--the sensitivity was low (see Table 72). Fully 71 percent of patients with night blindness, 32 percent with vitamin A-responsive Bitot's spots, and (most worrisome) 33 percent with active corneal disease failed to show definite staining. Furthermore, the fact that prevalence and pattern of staining in responsive and unresponsive lesions were identical precluded its value in distinguishing between the two. From a purely logistical viewpoint, trials in Study I indicated that vital staining slowed down the examination because children resisted having drops placed in their eyes, maintaining sterility was a problem, and anyone placing a firm pipette or needle in the vicinity of the cornea had to be highly trained and cautious.

F. Increasing Vitamin A Intake

It has already been suggested that correcting severe protein-energy malnutrition and systemic illnesses, identifying and treating cases of clinical and subclinical xerophthalmia, and preventing measles should help prevent nutritional blindness. Since vitamin A deficiency is the final common pathway for nutritional blindness, however, programs that improve vitamin A status, especially among those most deficient, should have a significant impact on the problem. The project addressed three approaches that may prove to be valuable, alone or in combination, in different areas of the country and segments of the population: (1) encourage intake of natural dietary sources of vitamin and provitamin A; (2) fortify some commonly eaten substance with vitamin A, and (3) periodically administer high-potency vitamin A capsules.

Dietary sources. Increasing consumption of glv is likely to be the most efficient and effective means of improving vitamin A status from natural dietary sources, at least among children age 2 and older. The difference in consumption of glv was the single most important dietary factor separating abnormals and controls. Glv are inexpensive and widely available, and most children, normal and abnormal, already eat some of them.

Widespread availability and use of glv was confirmed by family dietary patterns (see Table 73). Roughly 80 percent of households (whether or not they contained a xerophthalmic child) consumed glv at least once a day, and 99 percent did so at least once a week--this is even more frequent than the children's consumption of glv. Therefore, on the basis of all criteria, what appears to be needed is a nutritional education program directed toward increasing not only the frequency with which children age 2 and older eat glv already available and consumed by their families but the amount.

For younger children, the choice of program is less obvious. Consumption of glv was a less important determinant of xerophthalmia in this age group than was the consumption of fruits rich in beta carotene (mango and papaya) and breast feeding. There is little doubt that breast feeding should be encouraged for a host of reasons, and such

programs are already underway. Differences in consumption of fruit are important because far more children of this age group eat fruits than glv. Although fruits are apparently better accepted as part of a young child's diet, increasing their consumption may prove to be difficult because fruits rich in beta carotene are relatively expensive and in large part are seasonal. The survey was conducted during the mango season, so the rates for family consumption shown in Table 74, low as they are, are probably higher than at other times. Only 7 percent of families of abnormals ate fruits daily and 55 percent ate them weekly, compared with the much higher rates for glv.

The explanations given by parents or guardians of abnormal and normal children who never ate glv are shown in Tables 75 and 76. The rates in both are roughly similar, the larger number of normals providing more precise estimates. In large part, children under age 2 are not fed glv because mothers regard glv as inappropriate for young children and also do not know how to prepare glv for them. (The high rate of "other" reasons among children less than a year old reflects, in large part, their preweaning status). These results suggest that instructions on how to prepare glv for young children--coupled with messages that when properly prepared, glv, rather than being "too strong," are important for the young child's health--might increase consumption even in this age group.

By the time children were age 2, the most important reason cited for not giving them glv was the universal "the child does not like them." In the random sample, only 1.3 percent of all children who never ate glv and 0.3 percent of all children (10 percent and 1.4 percent, respectively, for abnormals) did not consume them because they were unavailable, thus confirming the conclusions drawn from the high rates of family consumption already presented.

Although the number of cases was small, the proportion of normal children who did not eat glv because they were unavailable was especially high in Aceh (13 percent; see Table 77). Among the few abnormal children who claimed not to eat glv because it was unavailable, three were from Aceh (20 percent of all cases of Bitot's spots in the province) and two from Central Java (4 percent of all cases of Bitot's spots in the

province). (See Table 78.) This suggests that the situation in Aceh is unique and that education alone may not be as effective there as elsewhere.

Fortification. Three centrally processed items--monosodium glutamate (MSG), wheat, and refined sugar-- were eaten by sufficiently large proportions of xerophthalmic children to be viewed as potentially suitable for vitamin A fortification. The product most frequently consumed on a regular basis (at least once a week) was MSG (see Tables 79 and 80). Roughly 70 percent of cases of Bitot's spots and normals in Study IV consumed MSG at least once a week; the rate increased with age, especially between years 0 and 1 and 1 and 2 ($p < .001$ among the larger number of normals). Rates for refined sugar and wheat were considerably lower (56 percent and 54 percent, respectively).

Rates of consumption among children with active corneal disease were lower than those among cases of Bitot's spots and normals: 46 percent of the former consumed MSG, 27 percent ate sugar, and 23 percent consumed wheat on a regular basis (at least once a week).

Although there was no difference in consumption by sex, there was by locale (see Table 81). Rates among normals and abnormals were roughly similar. Regular consumption of MSG was more uniform than that of the other potential carriers. Nonetheless, MSG was consumed by less than half the children in Aceh and Lombok, which suggests that fortification will not be as effective in these areas as in others and that other schemes will certainly need to be applied. Although these two areas were at highest risk, their populations--and hence their total contribution to the problem--is fortunately small.

Families as a whole consumed each of the three items more frequently than did the children (see Table 82).

Periodic massive dosing. Although addressing the question directly proved to be impractical, available data suggest that if all Indonesian children received 200,000 IU of vitamin A every four-to-six months, most nutritional blindness in Indonesia would probably be prevented. Whether a mass distribution program would actually be effective would depend primarily on whether the capsules reach the target population.

The first question is whether vitamin A can, by itself, prevent corneal disease, recognizing that many cases in Study II had accompanying protein-energy malnutrition and systemic illnesses that might interfere with the absorption and utilization of vitamin A. Since children with active corneal disease are more likely to be severely ill, malnourished, and vitamin A deficient than those who are only at risk of corneal disease, it seems reasonable to assume that if isolated vitamin A can heal corneal disease, it can surely prevent it. Demonstrating that this is indeed the case is difficult, however, because the vast majority of children in Study II were admitted to the hospital and received good food and general supportive care in addition to vitamin A therapy. In 22 instances where parents refused to allow hospitalization, the children received only oral vitamin A (seven received a single dose of 200,000 IU; 15 received a second dose the following day). Half (11 out of 22) had stromal disease (X3) and 45 percent (10 out of 22), severe protein-energy malnutrition (70 percent with gross edema). In all 22, the corneas improved or healed completely on this regimen. According to these findings, isolated vitamin A therapy should prevent corneal xerophthalmia. The next question is, for how long?

Three of the 22 cases are excluded from long-term follow-up. In one case suffering from severe protein-energy malnutrition (file 4), the cornea improved during early follow-up but the child died at three weeks. In the other two, the corneas had improved by day 3, when the parents finally agreed to hospitalization. The remaining 19 were followed, out of hospital, for 0.5 - 14 months (mean, 7.6 months; two-thirds, for at least six months). Only one of the children suffered an early, severe relapse, which began 16 to 23 days after his only dose of vitamin A. The child was severely malnourished (serum albumin, 1.5 gms/100 ml). When his condition was discovered, the child was immediately treated with a second oral dose. Although both corneas again began to heal and the parents finally agreed to hospitalization, the child died two days later.

Of the 18 survivors, two suffered relapses, neither of which occurred within six months of treatment. As in the case just described, both were severely malnourished. One developed mild corneal xerosis (X2)

eight months after a single capsule; the other, night blindness 13 months after two capsules.

In summary, under these extreme circumstances, all 22 children with active corneal xerophthalmia responded to isolated vitamin A therapy. Only one of the 19 (5 percent), with extended follow-up developed a severe early relapse, and he died and thus does not contribute to the blind population. None of the 18 survivors relapsed within six months of therapy (two-thirds were followed for at least that long). Children who received two capsules or were not severely malnourished fared better than their less fortunate peers.

Perhaps more pertinent to the question of the prevention provided by a single dose, instead of treatment of severe established disease, is the relapse rate among cases in Study III: all were cases of mild active disease (X1B), all received a single capsule, and all remained in their home environment. With the larger numbers available, a modified life-table analysis was performed (see Table 83). Cumulative relapse rates were 0 percent by six months, 5.3 percent by 10 months, and 11 percent by 14 months. All children were accounted for through home visits when the study ended, though not all returned for every monthly examination. Because none of the children developed corneal disease, it appears once again that the capsule was protective for a minimum of six months.

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TABLE 1

NIGHTBLINDNESS AND BITOT'S SPOTS AS INDEPENDENT SCREENING CRITERIA FOR XEROPHTHALMIA

(STUDY 1)

Clinical Status (1)	n	Mean Serum Vitamin A (ug/dl) (2)	SE	Proportion Total Cases Identified
XN	273	13.4	0.35	84%
X1B	132	12.6	0.46	41%
XN and/or X1B	325	13.4	0.31	100%

(1) XN includes cases with and without conjunctival xerosis (X1A), Bitot's spots, or X1B. X1B includes cases with and without nightblindness (XN).

(2) Serum vitamin A values were unavailable on 3 of 273 cases of nightblindness (XN), 2 of 132 cases of conjunctival xerosis with Bitot's spots (X1B) and 4 of 325 cases with either.

TABLE 2

SERUM VITAMIN A LEVEL BY CLINICAL STATUS

(STUDY 1)

Clinical Status[1]	n	Mean (ug/dl)	Percent of Individuals		
			Deficient (0-9ug/dl)	Low (10-19ug/dl)	Adeuqate (≥20ug/dl)
XN(+), X1B(-)	174	13.9	27	55	18
Controls	161	17.6			
XN(-), X1B(+)	51	13.4	31	57	12
Controls	45	17.1			
XN(+), X1B(+)	79	12.1	38	53	9
Controls	76	18.3			
Random Sample	268	20.0	9	38	53

(1) XN = nightblindness; X1B = conjunctival xerosis with Bitot's spots; XN (+), X1B (+) = XN and X1B coexistent in the same child.

Mean serum vitamin A and proportion of cases with "adequate" levels higher in less severe lesion: XN (+), X1B (-) > XN (-), X1B (+) > XN (+), X1B (+), $p < .05$ by linear trend.

TABLE 3

NIGHTBLINDNESS AMONG CASES OF VITAMIN A RESPONSIVE AND UNRESPONSIVE CONJUNCTIVAL XEROSIS* (STUDY III)

Test	Responsive I Cured	Responsive II Improved	Unresponsive III
History Available (n)	33	12	9
History Positive (%)	91	83	33
Exam Completed (n)	27	12	9
Exam Positive (%)	78	67	0

Statistical Significance:

	History:	Exam:
Overall distribution,	$p < .001$	$p < .001$
I vs. II ,	$p < .43$	$p < .46$
II vs. III,	$p < .05$	$p < .002$
I vs. III,	$p < .001$	$p < .001$

* See Table 5.

TABLE 4

XEROPHTHALMIA CLASSIFICATION **

*	XN	: Night blindness
	X1A	: Conjunctival xerosis
	X1B	: Bitot's spot with conjunctival xerosis
	X2	: Corneal xerosis
	X3A	: Corneal ulceration with xerosis
	X3B	: Keratomalacia
*	XF	: Xerophthalmic fundus
*	XS	: Corneal scars secondary to xerophthalmia

* Secondary sign. See text for modification in classification suggested by recent findings.

** Reference 10.

TABLE 5

CASES OF VITAMIN A RESPONSIVE AND UNRESPONSIVE CONJUNCTIVAL XEROSIS

(STUDY III)

Outcome	Number	Total
Responded Within 2 Months[a]		50
Cured	36	
Improved	14	
Unresponsive Within 3 Months		9
Indeterminate Response		24
Inadequate Early Followup	18	
Miscellaneous	6	
Total Cases Examined		83

a. Responsive lesions include those with definite but incomplete resolution ("improved") and those which totally disappeared ("cured") following one or more doses of 200,000 IU vitamin A.

TABLE 6

SPEED OF IMPROVEMENT IN RESPONSIVE CASES
OF CONJUNCTIVAL XEROSIS
(STUDY III)

Duration Since Therapy (days)	Cases Examined[a]	Cases Improved	
		n	%
1 - 4	20	11	55
5 - 7	28	28	100
8 - 14	4	4	100
15 - 21	3	3	100
22 - 31	3	2	67
32 - 62	2	2	100

a) Excludes cases already improved at an earlier examination.

TABLE 7

SPEED OF CURE IN CASES OF CONJUNCTIVAL XEROSIS
(STUDY III)

Duration Since Therapy (days)	Cases Examined[a]	Cases Cured[a]	
		n	%
1 - 4	16	0	.0
5 - 7	21	14	67
8 - 14	9	6	67
15 - 21	4	3	75
22 - 31	9	8	89
32 - 62	5	5	100

a) Excludes cases already cured at an earlier examination.

TABLE 8

INITIAL SERUM VITAMIN A LEVELS AMONG RESPONSIVE AND NONRESPONSIVE CASES OF CONJUNCTIVAL XEROSIS

(STUDY III)

	I Cured	II Improved	III Unresponsive
Number of subjects	22	9	4
Mean Vit.A (ug/dl)	13.5	10.1	29.5
SE	1.47	2.10	4.17

I plus II vs III, $p < .001$

TABLE 9

PROPORTION OF EYES WITH CONJUNCTIVAL XEROSIS IN WHICH THE NASAL QUADRANT IS INVOLVED

(STUDY III)

	I Cured	II Improved	III Unresponsive
Total eyes (n)	70	26	16
Eyes with nasal lesions			
(n)	46	15	1
(%)	66	58	6

Responsive versus unresponsive eyes, $p < .001$.

TABLE 10

AGE DISTRIBUTION OF RESPONSIVE AND UNRESPONSIVE CASES OF CONJUNCTIVAL XEROSIS

(STUDY III)

Age in Years Completed	Cured		Improved		Unresponsive	
	Number	Cumulative Percent	Number	Cumulative Percent	Number	Cumulative Percent
1	3	(8)				
2	11	(39)	3	(21)		
3	4	(50)	4	(50)		
4	5	(64)	1	(57)	1	(11)
5	3	(72)	2	(71)		(11)
6	6	(89)	1	(79)	1	(22)
7	2	(95)		(79)		(22)
8	1	(97)		(79)		(22)
9		(97)		(79)	1	(33)
≥10	1	(100)	3	(100)	6	(100)
Total	36		14		9	

Responsive cases younger than unresponsive, $p < .01$

TABLE 11

AGE DIFFERENCES IN THE PROPORTION OF CASES WITH UNRESPONSIVE CONJUNCTIVAL XEROSIS

(STUDY III)

Age (years)	Total Cases Number	Nonresponsive Cases Number	Percent
0 - 5	37	1	3
6 - 9	12	2	17
≥10	10	6	60

Younger cases were more likely to be responsive than older ones. ($p < .001$ by linear trend)

TABLE 12

SYMMETRY OF TEMPORAL AND NASAL LESIONS IN ABNORMAL EYES WITH RESPONSIVE CONJUNCTIVAL XEROSIS (STUDY III)

Nasal Lesion	Temporal Lesion				
	None	X1A	X1B(F)	X1B(C)	Total
None	4	7	28	1	40
X1A		4	13		17
X1B (F)			40		40
X1B (C)				3	3
Total	4	11	81	4	100

X1B (F) is foamy Bitot's spot

X1B (C) is cheesy Bitot's spot

$p < .001$ by x^2 test of distribution

TABLE 13

PRESENCE OF INJECTION AND SEVERITY OF CORNEAL INVOLVEMENT IN THE TWO EYES OF PATIENTS WITH CONJUNCTIVAL XEROSIS IN ONLY ONE EYE (STUDY II)

Conjunctival Injection [a]			Severity of Corneal Lesion [b]		
Conjunctival Xerosis			Conjunctival Xerosis		
Present	Absent	$\triangle$ * [c]	Present	Absent	$\triangle$ * [d]
-	+	+	(X2)	(X2)	
+	+	0	Staphyloma		
-	+	+	(X2)	(X2)	
-	+	+	-	X3A	+
-	+	+	-	X3A	+
+	+	0	X2	X3A	+
-	+	+	X2	X3A	+
-	+	+	X2	X3A	+
+	-	-	X3A	-	-
-	+	+	X2	X3B	+
-	+	+	X2	X3B	+
-	+	+	X2	X3B	+
+	+	0	X3A	X3B	+
-	+	+	-	X3B	+
-	+	+	X2	X3B	+
+	+	0	X3A	X3B	+
-	+	+	-	X3B	+
-	+	+	X2	X3B	+
-	+	+	X2	X3B	+
-	+	+	X2	X3B	+

* $p < .001$

TABLE 13 (continued)

a. (+) indicates injection present; (-) indicates injection absent

b. Classification defined in Table 4

c. (+) indicates injection in nonxerotic eye, not in xerotic
(-) indicates injection in xerotic eye, not in nonxerotic
(0) indicates injection present or absent in both eyes

d. (+) indicates nonxerotic eye contains more severe corneal disease than xerotic
(-) indicates xerotic eye contains more severe corneal disease than nonxerotic

TABLE 14

RESPONSE TO THERAPY: 7th - 8th ROUND

(STUDY I)

Diagnosis		Treatment: Vitamin A	Treatment: Placebo
XIB	Total (n)	37	32
	Cured (n)	29	16
	Cured (%)*	78	50
XN	Total (n)	40	43
	Cured (n)	32	28
	Cured (%)	80	65

* $p < .05$

TABLE 15

FLUORESCEIN POSITIVE PUNCTATE KERATOPATHY

(STUDIES II/III)

Clinical Classification	Number* of Eyes	Percent Positive	Average Extent (1)	Average Density (2)
Controls	58	7	1.0	1.0
XN: history positive exam negative	18	22	1.0	1.0
XN: history positive exam positive	10	60	1.3	1.7
X1A, 1B	63	75	1.9	1.9
X2	47	100	3.5	2.2

(1) Graded: 1=infero-nasal quadrant; 2=inferior 1/2 of cornea; 3=inferior 3/4 of cornea; 4=entire corneal surface

(2) Graded: 1=mild; 2=moderate; 3=heavy

* Numbers smaller then elsewhere because analysis was conducted early in study, before enrolment for other purposes was completed.

TABLE 16

RESPONSE OF PUNCTATE KERATOPATHY

TO 200,000 IU VITAMIN A

(STUDY III)

Duration since Treatment	Number of Eyes	Percent Improved	Percent Cured	Total Percent Improved or Cured
1 - 3 Days	20	40	0	40
4 - 7 Days	24	75	25	100
2 Weeks	20	20	80	100
1 Month	26	-	100	100

TABLE 17

PRESENCE OF GOBLET CELLS IN PRE- AND POST-TREATMENT CONJUNCTIVAL BIOPSIES (STUDY III)

Time of Biopsy	Location			
	Temporal		Inferonasal	
	Total (n)	Present (n)	Total (n)	Present (n)
Pretreatment	8	0	7	0
Postreatment (7 days)	3	0	1	0
Postreatment (14 days)	1	0	1	1
Postreatment ($\geq$ 1 month)	4	1	3	2

TABLE 18

SEX DISTRIBUTION OF CORNEAL CASES (X2/X3)

(STUDY II)

Diagnostic Classification (file)	Sex				Total
	Male		Female		
	n	(%)	n	(%)	n
1	I2	(50)	12	(50)	24
2	12	(50)	12	(50)	24
3	4	(80)	1	(20)	5
4	22	(49)	23	(51)	45
5	4	(80)	1	(20)	5
6	18	(53)	16	(47)	34
7	8	(61)	5	(39)	I3
8	6	(50)	6	(50)	12
Total	86	(53)	76	(47)	162

TABLE 19

AGE DISTRIBUTION OF CORNEAL CASES (X2/X3)

(STUDY II)

File	Total n	Age in Years (Percent of total in file) 0	1	2	3	4	5	≥6
1	24	0	8	21	33	21	8	8
2	24	0	13	42	17	17	8	4
3	5	0	0	60	20	20	0	0
4	45	4	11	42	16	13	9	4
5	5	0	0	60	40	0	0	0
6	34	15	24	29	15	15	3	0
7	13	23	31	23	8	15	0	0
8	12	17	25	8	17	8	8	17
Total	162	7	15	33	19	15	6	4

TABLE 20

PERCENT OF CASES BELOW AGE 2
BY SEVERITY OF CORNEAL INVOLVEMENT
(STUDY II)

Severity (file)	Percent of cases in file by Age (Years)		
	0	1	Total < 2 years
1-3	0	9.4	9.4
4-5	4.0	10.0	14.0
6	14.7	23.5	38.2
7-8	20.0	28.0	48.0

Proportion of cases less than 2 years of age increases with the severity of corneal involvement. ($p < .001$ by test for linear trend)

TABLE 21

SERUM VITAMIN A IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	n	Serum Vitamin A (ug/dl) $\bar{u}$	SE
1-3	26	8.2	0.94
4-5	32	7.2	0.70
6	25	5.4	0.72
7-8	15	5.2	1.01

$r = 0.9637$, $p < .01$; $b = 9.2$, $m = -1.08$

TABLE 22

DISTRIBUTION OF VITAMIN A LEVELS IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	n	Percent Distribution by Serum Vitamin A Level (ug/dl)			
		<10	10-14	15-19	≥ 20
1-3	26	61.5	26.9	7.7	3.8[a]
4-5	32	68.8	28.1	3.1	0.0
6	25	92.0	4.0	4.0	0.0
7-8	15	80.0	20.0	0.0	0.0
Total	98	74.5	20.4	4.1	1.0[a]

a. Represents a single borderline case, serum vitamin A = 21 ug/dl

TABLE 23

SERUM HOLO-RBP IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	n	Holo-RBP (ug/ml) $\bar{u}$	SE
1-3	38	1.13	0.22
4-5	28	1.00	0.23
6	15	1.33	0.31
7-8	14	1.07	0.22

TABLE 24

WEIGHT FOR HEIGHT OF CORNEAL CASES (X2/X3)

(STUDY II)

File	n	% Distribution by Percent of Standard[a]				
		≥90	80-89	70-79	60-69	<60
1-3	53	32.1	30.2	30.2	3.8	3.8
4-5	49	20.4	38.8	32.7	8.2	0.0
6	32	12.5	34.4	50.0	0.0	3.1
7-8	25	8.0	28.0	24.0	24.0	16.0
Total	159	20.8	33.3	34.0	7.5	4.4

a. Standards adapted from Jelliffe (20). Degree of wasting correlated with severity of corneal involvement, $p < .02$ by linear trend.

TABLE 25

PREVALENCE OF EDEMA IN CORNEA CASES (X2/X3)

(STUDY II)

File	Total n	Edema Present n	Edema Present %
1-3	53	10	18.9
4-5	50	15	30.0
6	30	9	30.0
7-8	24	12	50.0
Total	157	46	29.3

Files 1-6 versus 7-8: $p < .05$.

TABLE 26

SERUM ALBUMIN IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	n	Serum Albumin (gms/dl) $\bar{u}$	SE
1-3	53	3.20	.07
4-5	48	3.12	.08
6	33	3.07	.09
7-8	15	2.65	.15

Files 1-6 versus 7-8: $p < .01$

TABLE 27

DISTRIBUTION OF ALBUMIN LEVELS IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	Total n	Percent distribution Serum Albumin (gms/dl) ≥3.5	3.4-3.0	2.9-2.5	2.4-2.0	<2.0
1-3	53	35.8	34.0	24.5	3.8	1.9
4-5	48	29.2	35.4	25.0	6.3	4.2
6	33	27.3	27.3	36.4	6.0	3.0
7-8	25	20.0	4.0	28.0	44.0	4.0
Total	159	29,6	28.3	27.7	11.3	3.1

TABLE 28

SERUM TRANSFERRIN IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	n	Serum Transferrin (mg/dl) $\bar{u}$	SE
1-3	47	151.3	13.4
4-5	45	128.6	12.0
6	30	135.9	18.3
7-8	22	75.4	15.1

File 1-6 versus 7-8, $p < .01$.

TABLE 29

DISTRIBUTION OF TRANSFERRIN LEVELS IN CORNEAL XEROPHTHALMIA

(STUDY II)

File	Total n	Percent distribution Serum Transferrin (mg/dl) ≥200	199 -150	149 -100	99 -50	<50
1-3	47	36.2	12.8	17.0	12.8	21.3
4-5	45	17.8	17.8	31.1	13.3	20.0
6	30	26.7	13.3	20.0	16.7	23.3
7-8	22	9.1	4.5	9.1	27.3	50.0
Total	144	24.3	13.2	20.8	16.0	25.7

TABLE 30

PREVALENCE OF POSITIVE BACTERIAL CULTURES

(STUDY II)

Corneal Status	Total n	Percent of Eyes with Positive Cultures			
		Pseudom.	Micro. aur. Coag +	E. coli	Total Positive
MC	50	24	24	4	46
X2	117	25	30	9	53
X3A	65	31	28	14	60
X3A/B	44	36	23	11	57
X3B	35	31	34	11	54
X2/MC		1.04	1.25	2.25	1.15
X3A/X2		1.24	0.93	1.56	1.13
X3A(B)/X2		1.44	0.77	1.22	1.08
X3B/X2		1.24	1.13	1.22	1.02

TABLE 31

PREVALENCE OF XEROPHTHALMIC RETINOPATHY

(STUDIES II/III)

Age in Years	X1			X2		
	Total n	Positive[a] n	%	Total n	Positive[b] n	%
0	0	0	-	0	0	-
1	3	0	-	5	1	20
2	14	0	-	12	1	8
3	8	0	-	11	2	18
4	6	1	17	8	3	38
5	5	1	20	4	1	25
≥6	14	6	43	3	2	67
Total	50	8	16	43	11	26

a. Difference in prevalence between those below 4 and those older $p < .004$ by Fisher's Exact Test. An additional 3 cases had rare, fine, peripheral lesions of questionable significance (one each at ages 2, 3 and 4).

b. Difference in prevalence between those below 4 and older $.1 > p > .05$. An additional questionable case was 1 year old.

TABLE 32

COMPARABILITY OF TREATMENT GROUPS

(STUDY II)

	Oral		Parenteral	
	n	(%)	n	(%)
Total Eyes	88	(100)	58	(100)
Hospitalized	67	(76)	45	(78)
Clinical Diagnosis				
X2	50	(57)	38	(66)
X3A	26	(30)	9	(16)
X3B[a]	12	(14)	11	(19)
Diarrhea	35	(40)	20	(34)
PEM[b]	47	(53)	30	(52)
Mortality	8	(9)	3	(2)

a. Eyes with limbal to limbal necrosis excluded.

b. Protein-energy malnutrition defined by the presence of one or more of the following: serum albumin < 3.0 gms/dl or transferrin < 50 mg/dl; weight for height $< 70\%$ of standard; pedal edema.

TABLE 33

CLINICAL RESPONSE OF CORNEAL LESION IN ALL CASES

(STUDY II)

Days Since Therapy		Worse		Static		Improved		Cured		Total	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)[a]
1	Oral x 2	3	(6)	29	(62)	15	(32)	-	-	47	(53)
	IM + Oral	7	(23)	16	(53)	7	(23)	-	-	30	(52)
2-4	Oral x 2	7	(10)	11	(16)	39	(57)	12	(17)	69	(78)
	IM + Oral	3	(7)	14	(30)	23	(50)	6	(13)	46	(79)
6-8	Oral x 2	-	(-)	4	(6)	34	(51)	29	(43)	67	(76)
	IM + Oral	2	(4)	-	(-)	29	(55)	22	(42)	53	(91)
12-16	Oral x 2	-	(-)	1	(2)	12	(24)	36	(73)	49	(56)
	IM + Oral	2	(5)	0	(0)	11	(27)	28	(68)	41	(71)

a: Percent of all eyes in series examined in the interval.

TABLE 34

CLINICAL RESPONSE OF CORNEAL LESIONS IN CASES WITH DIARRHEA

(STUDY II)

Days Since Therapy		Worse		Static		Improved		Cured		Total	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)[a]
1	Oral x 2	1	(7)	12	(80)	2	(13)	-	(-)	15	(43)
	IM + Oral	3	(30)	5	(50)	2	(20)	-	(-)	10	(48)
2-4	Oral x 2	2	(7)	5	(17)	20	(70)	2	(7)	29	(83)
	IM + Oral	-	(-)	7	(39)	7	(39)	4	(22)	18	(86)
6-8	Oral x 2	-	(-)	1	(4)	19	(68)	8	(29)	28	(80)
	IM + Oral	-	(-)	-	(-)	14	(74)	5	(26)	19	(91)
12-16	Oral x 2	-	(-)	-	(-)	5	(24)	16	(76)	21	(60)
	IM + Oral	2	(11)	-	(-)	6	(32)	11	(58)	19	(91)

a. Percent of all eyes in series examined in the interval.

TABLE 35

CLINICAL RESPONSE OF CORNEAL LESIONS IN CASES WITH PEM[a]

(STUDY II)

Days Since Therapy		Worse		Static		Improved		Cured		Total	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)[b]
1	Oral x 2	2	(10)	12	(57)	7	(33)	-	(-)	21	(45)
	IM + Oral	5	(24)	12	(57)	4	(19)	-	(-)	21	(70)
2-4	Oral x 2	7	(18)	6	(15)	24	(62)	2	(5)	39	(83)
	IM + Oral	3	(12)	8	(32)	12	(48)	2	(8)	25	(83)
6-8	Oral x 2	-	(-)	4	(12)	19	(56)	11	(32)	34	(72)
	IM + Oral	2	(7)	-	(-)	20	(69)	7	(24)	29	(97)
12-16	Oral x 2	-	(-)	1	(3)	9	(31)	19	(66)	29	(62)
		2	(8)	-	(-)	8	(33)	14	(58)	24	(80)

a. PEM defined as one or more of the following: serum albumin < 3.0 gms/dl or transferrin < 50 mg/dl; weight for height $< 70\%$ of standard; pedal edema.

b. Percent of all eyes in series examined in the interval.

TABLE 36

SERUM VITAMIN A AND HOLO-RBP LEVELS

(STUDY II)

Time Since Initial Dose		Vitamin A (ug/dl) Oral	Vitamin A (ug/dl) IM	Holo-RBP (ug/ml) Oral	Holo-RBP (ug/ml) IM
0 Hours	$\bar{u}$	6.8	6.1	1.2	1.3
	SD	3.9	3.8	1.4	1.8
	n	35	16	35	29
4 Hours	$\bar{u}$	33.6	47.6	19.5	15.1
	SD	26.9	36.4	15.1	10.2
	n	36	16	23	11
1 Day	$\bar{u}$	**22.1	107.7	*12.1	20.0
	SD	24.2	46.2	10.0	9.8
	n	35	10	22	13
3 Days	$\bar{u}$	**28.4	152.8	18.6	21.6
	SD	34.1	86.5	12.4	9.8
	n	37	17	18	15
7 Days	$\bar{u}$	**22.9	53.0	24.7	27.4
	SD	8.0	39.8	10.1	16.3
	n	37	18	20	16

* Difference between oral and parenteral (IM) group statistically significant at $p < .05$; ** at $p < .001$.

TABLE 37

HOLO-RBP RESPONSE BY SERUM ALBUMIN IN CORNEAL XEROPHTHALMIA (STUDY II)

Time Since Dose (hours)		Serum Albumin (gms/100 ml) ≥3.5	3.4-3.0	2.9-2.5	<2.5
0	n	9	6	6	6
	$\bar{u}$	1.7	1.3	0.3	1.3
	SD	1.4	1.2	0.5	1.0
0-4	n	9	6	6	4
	$\bar{u}_{\Delta}$[a]	+26.2	+14.5	+8.7	+5.8
	SD	17.2	3.4	5.0	1.7
4-24	n	10	4	7	3
	$\bar{u}_{\Delta}$[a]	-10.7	-8.0	-3.6	+0.3
	SD	15.2	4.2	6.0	3.2

a) $\bar{u}_{\Delta}$ are all paired comparisons. Cases at 0 hours are those available for paired comparsion at 4 hours.

u_{Δ} correlated with serum albumin category:

change at 0-4 hours, $r = .9586$, $p < .05$; $m = -6.7$, $b = 30.6$

change at 4-24 hours, $r = .9957$, $p < .01$; $m = 3.7$, $b = -14.9$

TABLE 38

ANNUAL INCIDENCE ACTIVE CORNEAL XEROPHTHALMIA (X2/X3)

(STUDY 1 ROUNDS 2-5)

Village	No. of Cases	METHOD I		METHOD II	
		Mean No. Examined	Annual Incidence per 1000	Mean No. Eligible for Exam	Annual Incidence Per 1000
Citalang	2	900	2.2	1445	1.4
Cikao	1	202	5.0	283	3.5
Cilegong	1	239	4.2	357	2.8
Kembang	1	187	5.3	276	3.6
Gandasoli	8	793	10.1	1146	7.0
Citeko	3	453	6.6	1088	2.8
T o t a l	16	2773	5.8	4595	3.5
$CL_{95\%}$			3.0-8.6		1.8-5.2

Method I : Denominator is number of children examined at each round who were also examined, and found to be free of corneal disease, during the preceeding round, averaged over the 4 rounds (2-5) constituting a complete annual cycle. See text.

Method II: Denominator is average number of children eligible for examination at each round, regardless of whether or not they were ever examined. See text.

TABLE 39

AVERAGE PREVALENCE ACTIVE CORNEAL DISEASE (X2/X3)

(STUDY I, Rounds 2-5)

Village	Cases n	Examinations n	Prevalence (per 10,000)
Citalang	2	4260	4.7
Cikao	1	929	10.8
Cilegong	1	1124	8.9
Kembang	1	883	11.3
Gandasoli	8	3701	21.6
Citeko	3	2438	12.3
T o t a l	16	13,335	12.0

TABLE 40

PREVALENCE, INCIDENCE AND SPONTANEOUS CURE RATES FOR NONCORNEAL XEROPHTHALMIA (STUDY I)

Clinical Round	Prevalence %	Incidence %	Spontaneous Cure (%)
1	7.4	N.A.	N.A.
2	5.7	2.7	53.2
3	4.8	2.2	47.8
4	4.1	1.7	47.0
5	4.3	2.2	43.1
6	3.9	1.8	52.4
7	3.8	2.3	58.6

Noncorneal xerophthalmia includes cases of X1B (Bitot's spots with conjunctival xerosis) and/or XN (a history of nightblindness). Average interval between clinical rounds was 3 months. (Hand tabulated data.)

TABLE 41

ZONAL PREVALENCE XEROPHTHALMIA

(STUDY IV)

Zone	Families	Children	Bitot's spot		X2-X3		XS	
	n	n	n	%	n	per 10,000	n	per 10,000
West Java								
Rural	2759	4147	62	1.5	4	9.6	9	21.7
Urban	309	499	10	2.0	-	0.0	1	20.0
Central Java								
Rural	2952	4577	45	1.0	2	4.4	7	15.3
Urban	1133	1812	26	1.4	-	0.0	-	0.0
East Java								
Rural	2756	3949	31	0.8	-	0.0	-	0.0
Urban*	559	978	6	0.6	1	10.2	2	20.4
Sumatra								
Rural	2393	4267	38	0.9	6	14.1	7	16.4
Urban	711	1401	5	0.4	-	0.0	-	0.0
Sulawesi								
Rural	2010	3378	17	0.5	1	2.7	4	11.8
Urban	527	892	10	1.1	-	0.0	2	22.4

* Surabaya only. Malang, without a slum population and no xerophthalmia in the middle class community studied, is omitted.

TABLE 41 (continued)

Zone	Families n	Children n	Bitot's Spot n	Bitot's Spot %	X2-X3 n	X2-X3 per 10,000	XS n	XS per 10,000
Composite (#6)								
Bali								
Rural	774	1326	11	0.8	1	7.5	3	22.6
Urban	293	507	3	0.6	-	0.0	-	0.0
Lombok								
Rural	1405	2353	37	1.6	5	21.2	5	21.2
Kalimantan								
Rural	1159	2056	15	0.7	1	4.9	2	9.7
Urban	983	1856	14	0.8	-	0.0	3	16.2
Ambon								
Rural	556	1031	21	2.0	-	0.0	2	19.4
Jakarta								
urban	405	686	5	0.7	-	0.0	-	0.0

TABLE 42

INTRAZONAL RURAL PREVALENCE (STUDY IV)

PROVINCIAL RATES FOR SUMATRA, SULAWESI AND KALIMANTAN

	Zone	Children n	Bitot's Spot n	Bitot's Spot %	X2-X3 n	X2-X3 per 10,000	XS n	XS per 10,000
Sumatra	Aceh	620	15	2.4	3	48.4	1	16.1
	Bengkulu	460	3	0.7	1	21.7	1	21.7
	W. Sumatra	611	8	1.3	1	16.4	1	16.4
	S. Sumatra	606	2	0.3	1	16.5	3	49.5
	N. Sumatra	463	2	0.4	-	0.0	1	21.6
	Jambi	550	5	0.9	-	0.0	-	0.0
	Riau	467	2	0.4	-	0.0	-	0.0
	Lampung	490	1	0.2	-	0.0	-	0.0
Sulawesi	S. Sulawesi	1240	5	0.4	1	8.1	1	8.1
	S.E. Sulawesi	809	4	0.5	-	0.0	3	3.7
	C. Sulawesi	477	5	1.0	-	0.0	-	0.0
	N. Sulawesi	852	3	0.4	-	0.0	-	0.0
Kalimantan	C. Kalimantan	450	3	0.7	1	22.2	-	0.0
	W. Kalimantan	460	2	0.4	-	0.0	1	21.7
	S. Kalimantan	680	10	1.5	-	0.0	1	14.7
	E. Kalimantan	466	0	0.0	-	0.0	-	0.0

TABLE 43

INTRAZONAL URBAN PREVALENCE (STUDY IV)

SLUM AREAS OF SELECTED MUNICIPALITIES IN SUMATRA, SULAWESI AND KALIMANTAN

	Site	No. Children	Bitot's spot n	Bitot's spot %	X2-X3 n	X2-X3 per 10,000	XS #	XS per 10,000
Sumatra	Medan (N. Sumatra)	477	1	0.2	-	0.0	-	0.0
	Padang (W. Sumatra)	460	0	0.0	-	0.0	-	0.0
	Palembang (S. Sumatra)	464	4	0.9	-	0.0	-	0.0
Sulawesi	Menado (N. Sulawesi)	408	3	0.7	-	0.0	1	24.5
	Ujunpandang (S. Sulawesi)	484	7	1.4	-	0.0	1	20.7
Kalimantan	Balikpapan (E. Kalimantan)	574	2	0.3	-	0.0	1	17.4
	Banjarmasin (S. Kalimantan)	511	4	0.8	-	0.0	1	19.6
	Palangkaraya (C. Kalimantan)	445	7	1.7	-	0.0	1	22.5
	Pontianak (W. Kalimantan)	326	1	0.3	-	0.0	0	0.0

TABLE 44

CONFIDENCE LIMITS OF XEROPHTHALMIA PREVALENCE DATA

IN RURAL AREAS

(STUDY IV)

Zone	X1B (per 100)		X2/X3 (per 10,000)		XS (per 10,000)	
	p	$CL_{95\%}$	p	$CL_{95\%}$	p	$CL_{95\%}$
W. Java	1.5	0.9-2.1	10	0-21	22	8-36
C. Java	1.0	0.6-1.4	4	0-10	15	2-28
E. Java	0.8	0.4-1.1	0	-	0	-
Bali	0.8	0.2-1.5	8	0-23	23	0-48
Lombok	1.6	0.8-2.3	21	3-39	21	3-39
Sumatra	0.9	0.5-1.3	14	4-24	16	4-28
Sulawesi	0.5	0.2-0.8	3	0- 9	12	2-22
Kalimantan	0.7	0.2-1.2	5	0-15	10	0-24
Ambon	2.0	0.3-3.7	0	-	19	0-47
Indonesia (weighted)	1.0	0.9-1.1	6	3-10	13	9-18

TABLE 45

TECHNIQUE FOR ESTIMATING OVERALL PREVALENCE (X2/X3)

WITHIN SURVEYED RURAL INDONESIA

$$p = \sum \frac{Nh}{N} (Ph)$$

where: N_h = size of stratum

N = size of population

Ph = prevalence in that statum

Qh = 1 - Ph

$$SE = \sqrt{\sum \left[\frac{Nh}{N}\right]^2 \left[\frac{Ph\ Qh}{Nh}\right]}$$

Zone[a]	Nh/N Proportion Total Population	Ph Prevalence X2/X3 per 10,000	Contribution to Weighted Prevalence
W. Java	.190	9.6	1.824
C. Java	.214	4.4	0.942
E. Java	.224	0.0	0.000
Sumatra	.183	14.1	2.580
Kalimantan	.045	4.9	0.221
Sulawesi	.075	2.7	0.203
Other Islands	.069	9.6	0.662
Total	1.000		6.432

$$SE = \sqrt{257 \times 10^{-10}} = 1.6 \text{ per } 10{,}000$$

a) DKI Jakarta and Irian Jaya omitted from tabulation. D.I. Jogjakarta included in Central Java. Prevalence rate for "other islands" is mean rate for Ambon/Bali/Lombok.

TABLE 46

MORTALITY AMONG CASES OF ACTIVE CORNEAL DISEASE

(STUDY II)

Duration of Followup	Not Severely Malnourished				Severely Malnourished[a]			
	Total	Died			Total	Died		
	n	n	(%)	Cum.%	n	n	(%)	Cum.%
1 week	96	0			65	4	(6.2)	6.2
2 week	92	0			59	2	(3.4)	9.6
1 Month	90	1	(1.1)	1.1	57	4	(7.0)	16.6
2 Month	81	0		1.1	50	2	(4.0)	20.6
3-4 Month	74	2	(2,7)	3.8	48	1	(2.1)	22.7
5-6 Month	55	0		3.8	45	0		22.7
7-8 Month	41	0		3.8	33	1	(3.0)	25.7
9-10 Month	28	0		3.8	24	0		25.7
11-12 Month	24	0		3.8	18	0		25.7
13-14 Month	14	0		3.8	11	0		25.7
Total		3		3.8		14		25.7

a. Severe Malnutrition defined as any of the following: edema, albumin $\leq$2.5 gms/100 ml, or weight for height $<$ 70% of standard.

Difference in mortality between the two groups, $p < .01$.

TABLE 47

AGE DISTRIBUTION OF CORNEAL CASES

(STUDY IV)

Age (years)	Active Disease (X2/X3)		Old Disease (XS)			
			At Onset[a]		At Present	
	n	(%)	n	(%)	n	(%)
0	1	(5)	10	(23)	0	(0)
1	3	(14)	9	(20)	3	(6)
2	9	(41)	14	(32)	6	(13)
3	6	(27)	9	(20)	14	(30)
4	2	(9)	2	(5)	14	(30)
5	1	(5)	0	(0)	10	(21)

a. Three, with unkown age of onset, excluded.

TABLE 48

AGE DISTRIBUTION OF STUDY POPULATION

STUDY IV (40/41)

Age (years)	Males		Females		Total	
	n	%	n	%	n	%
0	2905	15.7	2907	16.5	5812	16.1
1	2934	15.9	2842	16.2	5776	16.0
2	3140	17.0	2852	16.2	5992	16.6
3	3110	16.8	2989	17.0	6099	16.9
4	2835	15.3	2767	15.7	5602	15.5
5	3237	17.5	2929	16.6	6166	17.1
unkn.(1)	314	1.7	299	1.7	613	1.7
Total	18,475	99.9	17,585	99.9	36,060	99.9

(1) Under 6 years but age unknown or miscoded.

TABLE 49

PREVALENCE OF BITOT'S SPOTS

STUDY IV (40/41)

Age (years)	Male		Female		Total	
	n	%	n	%	n	%
0	0	0.00	1	0.03	1	0.02
1	15	0.51	10	0.35	25	0.43
2	48	1.53	22	0.77	70	1.17
3	63	2.03	31	1.04	94	1.54
4	44	1.55	26	0.94	70	1.25
5	57	1.76	35	1.19	92	1.49
unkn.	4	1.27	2	0.67	6	0.98
Total	231	1.25	127	0.72	358	0.99

Change in prevalence (sexes combined) for years 0-1, 1-2, and 2-3 all $p < .01$.

Overall prevalence, males versus females, $p < .001$.

TABLE 50

SEVERITY OF CORNEAL DISEASE AMONG ALL ABNORMALS (X2/X3) AND THOSE WITH MATCHED CONTROLS (STUDY II)

File	Percent Distribution by File	
	All Abnormals (n=162)	Those with Matched Controls (n=33)
1	14.8	15.2
2	14.8	15.2
3	3.1	3.0
4	27.8	33.3
5	3.1	0.0
6	21.0	12.1
7	8.0	18.2
8	7.4	3.0
1-3	32.7	33.3
4-5	30.9	33.3
6-8	36.4	33.3

TABLE 51

MEAN PERCENT OF STANDARD[a] WEIGHT FOR HEIGHT BY AGE AND CLINICAL STATUS

(STUDY IV)

Age (years)		Clinical Classification		
		Bitot's Spots	Matched Controls	Normal
0	n	1	2	5630
	$\bar{u}$	100	102	99
1	n	25	24	5590
	$\bar{u}$	86	94	92
2	n	70	64	5704
	$\bar{u}$	94	94	93
3	n	94	84	5773
	$\bar{u}$	95	96	96
4	n	70	67	5327
	$\bar{u}$	98	99	97
5	n	97	98	6425
	$\bar{u}$	98	97	96
Total	n	357	339	34,449
	$\bar{u}$	95	96	95

a. Standards adapted from (20), with extrapolation down to 45.5 cm

TABLE 52

DISTRIBUTION WEIGHT FOR HEIGHT BY DECILES OF STANDARD[a]

(STUDY IV)

Age (years)	Clinical Class.	Total n	Distribution (percent of total) Decile 5/6	7	8	≥ 9
1	X1B	25	12.0	20.0	24.0	44.0
	MC	24	-	8.3	29.2	62.5
	N	5589	1.2	8.1	34.3	56.4
2	X1B	70	-	4.3	35.7	60.0
	MC	64	1.6	4.7	26.6	67.2
	N	5704	0.8	4.3	30.1	64.7
3	X1B	94	1.1	5.3	23.4	70.2
	MC	84	-	2.4	20.4	77.4
	N	5773	0.5	2.5	20.5	76.5
4	X1B	70	-	1.4	15.7	82.9
	MC	67	-	-	20.9	79.1
	N	5327	0.3	1.4	18.3	80.0
5	X1B	97	-	1.0	10.3	88.7
	MC	98	-	-	15.3	84.7
	N	6425	0.3	1.6	20.6	77.4

a. Standard adapted from (20) with extrapolation down to 45.5 cm.

TABLE 53

PAIRWISE DIFFERENCE IN PERCENT STANDARD HEIGHT FOR AGE[a] BY SEVERITY OF CORNEAL INVOLVEMENT

(STUDY II)

Comparison	n	$\bar{u}_{\Delta}$	SE
X2-MC	8	-3.95	2.43
X3A-MC	10	-2.72	2.43
X3B-MC	9	-1.62	1.86
Total X-MC	27	-2.72	1.27

$r = .9995$, $p < .001$; $b = -1.164$, $m = 5.09$

a. Adapted from (20).

TABLE 54

HEIGHT FOR AGE BY CLINICAL DIAGNOSIS

(STUDY IV)

Age (years)	Number				Mean (in cm)			
	X2/X3	X1B	MC	N	X2/X3	X1B	MC	N
0	1	1	2	5645	48.0	48.0	75.0	63.6
1	3	25	24	5596	64.7	71.2	73.3	72.7
2	9	70	64	5713	75.4	77.9	79.6	79.7
3	6	94	84	5782	78.8	83.9	86.0	86.5
4	2	70	67	5332	80.5	91.0	93.4	92.7
5	1	98	98	6427	94.0	97.6	100.5	99.8

X2/X3; X1B, and X1B: MC, $p < .01$.

TABLE 55

HISTORY OF DIARRHEA[a] BY CLINICAL STATUS

(STUDY IV)

Age (in years)	Number in Class			Percent with Positive History[b]					
				Past Week			Past Month[c]		
	X1B	MC	N	X1B	MC	N	X1B	MC	N
0	1	2	5674	0.0	0.0	5.5	0.0	0.0	6.4
1	25	24	5607	12.0	16.7	7.6	18.2	20.1	11.8
2	70	64	5723	12.9*	3.1	5.7	16.4	20.9	11.5
3	94	85	5793	13.8*	4.7	3.9	16.0	11.2	10.6
4	70	67	5338	10.0*	1.5	2.7	12.7	12.1	9.3
5	92	92	5843	4.3	1.1	2.1	10.2	7.7	7.6
Unkn.	6	6	598	0.0	0.0	0.8	0.0	16.7	1.5

a) Defined as 4 or more loose stools in one day

b) Most recent episode

c) Excluding past week. Those positive in past week excluded from at risk group.

* X1B versus M.C.: $p < .05$. Overall rate during past week plus month, X1B versus M.C., $p < .01$; for past week, $p < .001$.

TABLE 56

HISTORY OF PASSING WORMS BY CLINICAL STATUS

(STUDY IV)

Age (in years)	Percent Distribution[a] Past Week X1B	MC	N	Past Month[b] X1B	MC	N	Ever X1B	MC	N
0[c]									
1	12.0	0.0	2.5	32.0	0.0	7.9	68.0	20.8	23.7
2	5.7	3.1	3.0	25.7	23.4	11.6	51.4	51.6	39.8
3	12.8	3.5	2.7	20.2	11.8	11.7	56.4	52.9	44.1
4	2.9	3.0	2.5	20.0	14.9	9.9	60.0	53.7	44.7
5	5.4	2.2	2.1	20.0	14.1	9.3	50.0	44.6	45.5
Unkn.	0.0	0.0	1.0	16.7	0.0	5.5	66.7	83.3	32.6

Abnormals versus Matched Controls: $p < .02$ overall; $p < .01$ for difference in positive rates during past week.

a. Number at risk same as in Table 56. Most recent episode listed.

b. Including within past week.

c. Only 1 abnormal, 2 matched controls: both with negative histories. Overall positive rate for normals, 3%

TABLE 57

PREVALENCE OF RESPIRATORY TRACT DISEASE

(STUDIES II/III)

Clinical Classification	Total Examined	Respiratory Disease	
	n	n	%
XI (Study III)	50	7	14.0
X2 (Files 1-3)	53	11	20.8
X3A (Files 4-5)	50	16	32.0
X3B (Files 6-8)	53	32	60.4

$p < .01$ for linear trend

TABLE 58

GENERAL CLINICAL CONDITION

(STUDIES II/III)

Ocular Status	Total n	% Distribution by Severity of Illness			
		None	Minimal	Moderate	Severe
XI	50	58	36	6	0
X2	48	44	19	21	17
X3A	46	30	9	46	15
X3B	47	9	15	23	53
X2-X3B	141	28	14	30	28

$p < .01$ for presence of illness, and presence of moderate plus severe illness, by linear trend.

TABLE 59

HISTORY OF RECENT MEASLES AMONG CASES OF CORNEAL DISEASE BY TIME OF ONSET

(STUDY II)

Corneal Cases Severity (file)	Total n	Onset of Measles[a] (n) ≤7days	≤2weeks	≤3weeks	≤1month	≤2months	Total with Measles n	Total with Measles %
1-3	53					1	1	1.9
4-5[b]	50						0	-
6-8	59	1	1	5	2	1	10	16.9

Difference in prevalence for files 1-5 versus 6-8, $p < .01$.

a. Mutually exclusive time intervals

b. 2 atypical cases excluded from file 4 entirely: one with measles onset at ≤ 7d, the other at ≤2w.

TABLE 60

HISTORY OF MEASLES DURING THE PAST MONTH

(STUDY IV)

Age (years)	Total Examined (n)			Percent Measles		
	X1B	MC	N	X1B	MC	N
0	1	2	5674	-	-	5.1
1	25	24	5607	8.0	8.3	6.0
2	70	64	5723	8.5	9.4	5.4
3	94	85	5793	7.5	3.5	4.4
4	70	67	5338	4.3	6.0	4.0
5	92	92	5843	3.3	-	3.2
Unkn.	6	6	598	-	16.7	3.0
Total	358	340	34576	5.9	4.8	4.7

TABLE 61

PREVALENCE OF BREAST FEEDING

(STUDY IV)

Age (years)	Number Examined			% Breast Fed		
	X1B	MC	N	X1B	MC	N
0	1	2	5674	-	100.0	94.3
1	25	24	5607	24.0	70.8	69.7
2	70	64	5723	14.2	28.2	31.9
3	94	85	5793	4.3	6.0	9.7
4	70	67	5338	1.4	1.5	3.8
5	92	92	5843	-	2.2	1.4
Unkn.	6	6	598	-	-	0.2
Total[a]	358	340	34576	5.9	13.2	14.9

X1B versus MC, $p < .001$.

a. Normals age adjusted to distribution of X1B/MC

TABLE 62

REASON BREAST FEEDING DISCONTINUED

(STUDY IV)

Reason	Clinical Classification (n)			Clinical Classification (%)		
	X1B	MC	N	X1B	MC	N
Mother Pregnant	126	102	7653	38.3	35.8	35.0
Mother Gave Birth	15	13	656	4.6	4.6	3.0
Child Sick	6	5	440	1.8	1.8	2.0
Child Seperated	2	1	233	0.6	0.4	1.1
Mother Working	2	2	399	0.6	0.7	1.8
No Milk	7	6	656	2.1	2.1	3.0
Not Needed	171	156	11810	52.0	54.7	54.1
Total	329	285	21847	100.0	100.0	100.0

TABLE 63

MEAN DIFFERENCE IN FREQUENCY OF FOOD CONSUMPTION BY PAIRWISE COMPARISON BETWEEN CORNEA CASES AND MATCHED CONTROLS[a]

(STUDY II)

		Food Item[b]							
		Liver	Meat	Eggs	Fish	Soy	GLV	Carrots	Fruit
$\bar{u}\,\Delta$[c]:		+.032	+.358	+.617*	+.467*	+.042	+.842*	+.875**	+.217
Consuming (n)[a]:									
1/week	X2/3	1	3	2	5	23	10*	0*	5
	MC	1	5	9	6	27	18	6	9
1/month	X2/3	3	12	14**	13	27	19*	6*	8
	MC	1	17	24	17	29	27	15	11
Ever	X2/3	5	21	21	17**	27	19*	11**	12
	MC	10	23	25	26	29	27	21	14

* = $p < .05$; ** $p < .01$ for difference between X1B and MC.

a. n = 30 pairs, so 30 X2/3 and 30 MC for comparison.

b. Fish = fresh fish; GLV = green leafy vegetables; fruit = mango/papaya.

c. See text for method of calculation: MC - X2/3.

TABLE 64

FREQUENCY OF CONSUMPTION OF GREEN LEAFY VEGETABLES

(STUDY IV)

Age (years)	Dx	Total n	% Distribution by Frequency of Consumption ≥1/day	≥1/week	≥1/month	<1/month
0	X1B	1				
	NRS[a]	1034	12	9	1	76
1	X1B	25	40	24	4	32
	NRS	1097	35	32	6	27
2*	X1B	70	23	43	16	19
	NRS	1017	43	41	6	10
3*	X1B	94	29	40	14	17
	NRS	1064	46	41	6	6
4*	X1B	70	40	33	10	17
	NRS	937	47	40	5	7
5*	X1B	92	36	33	13	18
	NRS	997	47	38	7	7

* $p < .01$ by x^2, X1B versus NRS

a. "Normal Random Sample" (ie, random sample less abnormals and matched controls)

TABLE 65

FREQUENCY OF CONSUMPTION OF MANGO/PAPAYA

(STUDY IV)

Age (years)	Dx	Total n	% Distribution by Frequency of Consumption ≥1/day	≥1/week	≥1/month	<1/month
0	X1B	1				
	NRS[a]	1034	33	22	7	37
1*	X1B	25	16	20	40	24
	NRS	1097	27	40	23	11
2*	X1B	70	16	46	26	12
	NRS	1017	28	40	26	6
3	X1B	94	16	44	35	5
	NRS	1064	26	41	26	6
4	X1B	70	29	36	20	15
	NRS	937	27	43	25	5
5	X1B	92	23	37	30	10
	NRS	997	26	43	26	5

* $p < .05$ by x^2, X1B versus NRS

a. "Normal Random Sample" (ie. random sample less abnormal and matched controls.

TABLE 66

FREQUENCY OF CONSUMPTION OF EDIBLE OILS

(STUDY IV)

Age (years)	Dx	Total n	% Distribution by Frequency of Consumption			
			≥1/day	≥1/week	≥1/month	<1/month
0	X1B	1				
	NRS	1034	9	6	2	84
1	X1B	25	36	28	8	28
	NRS	1097	43	26	6	25
2	X1B	70	51	29	9	11
	NRS	1017	56	32	6	6
3*	X1B	94	47	31	13	10
	NRS	1064	56	31	6	6
4	X1B	70	53	33	7	11
	NRS	937	61	30	5	5
5	X1B	92	50	35	7	9
	NRS	997	62	28	6	4

* $p < .05$ by x^2, X1B versus NRS.

TABLE 67

FREQUENCY OF CONSUMPTION OF MEAT

(STUDY IV)

Age (years)	Dx	Total n	% Distribution by Frequency of Consumption			
			≥ 1/day	≥ 1/week	≥ 1/month	< 1/month
0	X1B	1				
	NRS	1034	2	3	3	92
1	X1B	25	0	12	24	64
	NRS	1097	2	14	24	59
2	X1B	70	3	7	29	62
	NRS	1017	2	17	34	46
3	X1B	94	2	11	37	50
	NRS	1064	4	19	35	42
4	X1B	70	1	17	30	51
	NRS	937	3	20	34	43
5*	X1B	92	1	9	39	51
	NRS	997	2	21	36	41

* $p < .05$ by x^2, X1B versus NRS.

TABLE 68

FREQUENCY OF CONSUMPTION OF FRESH FISH

(STUDY IV)

Age (years)	Dx	Males				Females			
		Total n	% Distribution ≥1/w	≥1/m	<1/m	Total n	% Distribution ≥1/w	≥1/m	<1/m
0	X1B	1							
	NRS	487	7	1	92	547	6	2	94
1	X1B	15	20	13	67	10	60	0	40
	NRS	552	39	10	51	545	38	11	51
2	X1B	48	38	13	50	22	54	9	36
	NRS	534	50	16	34	483	54	17	29
3	X1B	63	49	19	31	31	55	16	29
	NRS	542	58	16	26	522	53	19	28
4	X1B	44	53	23	15	26	57	19	23
	NRS	495	57	15	27	442	59	19	23
5	X1B	57	34	28	39	35	51	11	38
	NRS	496**	57	15	28	501	55	17	27

** $p < .01$ x^2, X1B versus NRS.

TABLE 69

FREQUENCY OF CONSUMPTION OF EGG

(STUDY IV)

Age (years)	Dx	Total n	% Distribution by Frequency of Consumption			
			≥1/day	≥1/week	≥1/month	<1/month
0	X1B	1				
	NRS	1034	2	10	6	83
1	X1B	25	8	16	20	56
	NRS	1097	8	30	21	42
2**	X1B	70	1	20	24	54
	NRS	1017	6	32	27	35
3*	X1B	94	2	26	28	45
	NRS	1064	6	35	26	33
4**	X1B	70	6	13	34	47
	NRS	937	4	36	30	30
5**	X1B	92	0	24	27	49
	NRS	997	5	35	27	33

* $p < .05$ by x^2, X1B versus NRS; **$p < .01$.

TABLE 70

PRINCIPLE OCCUPATION OF HEAD OF HOUSEHOLD

(STUDY IV)

Occupation	Distribution (n)			Distribution (%)		
	X1B	MC	N	X1B	MC	N
Farmer	141	141	14858	39	42	43
Servant	16	14	923	5	4	3
Laborer	123	79	8307	34	23	24
Government	22	37	3820	6	11	11
Military	4	16	837	1	5	2
Priv. Employee	11	19	2089	3	6	6
Small Business	35	30	3360	10	9	10
Industry	6	3	326	2	1	1
None/other	0	1	56	0	0	0
Total	358	340	34576	100	101	100

Percent laborers X1B versus MC or N, $p < .001$

TABLE 71

HISTORY OF NIGHTBLINDNESS (XN) AMONG CASES OF BITOT'S SPOTS (X1B) (STUDY IV)

Geographic Area	Cases of X1B n	History Positive for XN n	%
Urban	83	39	47.0
W. Java	62	38	61.3
C. Java	45	34	75.6
E. Java	31	4	12.9
Bali	11	3	27.3
Lombok	37	17	45.9
Sumatra	38	25	65.8
Sulawesi	17	7	41.2
Kalimantan	13	9	69.2
Ambon	21	2	9.5

TABLE 72

LISSAMINE GREEN STAINING OF PATIENTS WITH CLINICAL XEROPHTHALMIA AND CONTROLS (STUDIES II/III)

Clincial Status		Total Cases	Definite(+) 2 Eyes	Definite(+) 1 Eye	Indefinite(+) 1 or 2 Eyes	Negative 2 Eyes
Normal Controls	n	51	2	4	3	42
	(%)	(100)	(3.9)	(7.8)	(5.9)	(82.4)
Night Blind	n	14	3	1	2	8
	(%)	(99.9)	(21.4)	(7.1)	(14.3)	(57.1)
Nonresponsive Bitot's Spots	n	6	5	1	-	-
	(%)	(100)	(83.3)	(16.7)	-	-
Responsive Bitot's Spots and/or Conjunctival Xerosis	n	31	18	3	1	9
	(%)	(100)	(58.1)	(9.7)	(3.2)	(29.0)
Corneal Xerophthalmia	n	51	22	12	4	13
	(%)	(99.9)	(43.1)	(23.5)	(7.8)	(25.5)

TABLE 73

FAMILY CONSUMPTION OF GREEN LEAFY VEGETABLES

(STUDY IV)

Clinical Status	Total n[a]	% Distribution by Frequency of Consumption				
		≥1/d	≥1/w	≥1/m	<1/m	never
X1B	358	79.1	19.8	0.8	0.0	0.3
MC	340	81.5	17.4	1.2	0.0	0.0
N	34576	81.9	16.8	1.0	0.1	0.2

a. Family data for each child in study; some families are therefore included more than once.

TABLE 74

FAMILY CONSUMPTION OF MANGO/PAPAYA

(STUDY IV)

Clinical Status	Total n[a]	% Distribution by Frequency of Consumption				
		≥1/d	≥1/w	≥1/m	<1/m	never
X1B	358	6.7	48.0	33.8	4.2	7.3
MC	340	13.2	41.2	35.0	3.2	7.4
N	34576	11.4	49.4	29.3	3.2	6.7

a. Family data for each child in study; some families are therefore included more than once.

TABLE 75

REASON SOME CHILDREN NEVER EAT GREEN LEAFY VEGETABLES

RANDOM SAMPLE[a]

(STUDY IV)

Age (years)	Total[b] (n)	% Distribution by Reason					
		Not Bought	Not Available	Too Strong	Child Dislikes	Can't Cook	Other[c]
0	773	0.1	0.0	23.4	7.1	14.6	54.7
1	274	0.7	1.8	14.2	39.8	17.9	25.5
2	78	2.6	1.3	2.6	70.5	7.7	15.4
3	40	2.5	7.5	0.0	67.5	12.5	10.0
4	47	0.0	4.3	0.0	78.7	8.5	8.5
5	53	1.9	3.8	0.0	88.7	3.8	1.9

a. Entire random sample, including normals, abnormals and matched controls.

b. Children who never consume glv.

c. Vast majority of those under 2 years not yet weaned.

TABLE 76

REASON SOME CHILDREN NEVER EAT GREEN LEAFY VEGETABLES ABNORMALS (X1B) (STUDY IV)

Age (years)	Total[b] (n)	% Distribution by Reason					
		Not Bought	Not Available	Too Strong	Child Dislikes	Can't Cook	Other
0	0	-	-	-	-	-	-
1	6	0.0	0.0	0.0	66.7	16.7	16.7
2	10	0.0	10.0	0.0	60.0	10.0	20.0
3	13	0.0	7.7	0.0	69.2	7.7	15.4
4	9	0.0	11.1	0.0	88.9	0.0	0.0
5	13	0.0	15.4	0.0	69.2	7.7	7.7

a. Children who never consume glv.

TABLE 77

REGIONAL DIFFERENCES IN WHY SOME CHILDREN NEVER CONSUME GREEN LEAFY VEGETABLES (HIGH RISK RURAL AREAS) RANDOM SAMPLE[a] (STUDY IV)

Area	Total (n)	% Distribution by Reason					
		Not Bought	Not Avail.	Too Strong	Child Dislikes	Can't Cook	Other
Aceh	23	0.0	13.0	0.0	39.1	0.0	47.8
Bengkulu	15	0.0	0.0	0.0	26.7	13.3	60.0
Lombok	97	1.0	3.1	34.0	9.3	3.1	49.5
W. Java	150	0.0	0.7	22.7	26.0	10.0	40.7
C. Java	137	0.7	0.7	8.0	34.3	16.8	39.4
W. Sumatra	16	0.0	0.0	0.0	50.0	12.5	37.5
S. Sumatra	21	0.0	0.0	0.0	23.8	0.0	76.2
C. Kalimantan	24	4.2	0.0	4.2	58.3	0.0	33.3
Bali	46	0.0	0.0	30.4	13.0	6.5	50.0
S. Sulawesi	33	0.0	0.0	45.5	3.0	42.4	9.1
Ambon	28	0.0	0.0	64.3	3.6	32.1	0.0

a. Entire random sample, including normals, abnormals and matched controls.

TABLE 78

REGIONAL DIFFERENCES IN WHY SOME CHILDREN
NEVER CONSUME GREEN LEAFY VEGETABLES
(HIGH RISK RURAL AREAS)
ABNORMALS (X1B)
(STUDY IV)

Area	Total (n)	Distribution by Reason (n)					
		Not Bought	Not Avail.	Too Strong	Child Dislikes	Can't Cook	Other
Aceh	3	-	3	-	-	-	-
Bengkulu	1	-	-	-	1	-	-
Lombok	3	-	-	-	1	-	2
W. Java	9	-	-	-	8	-	1
C. Java	8	-	2	-	5	1	-
W. Sumatra	0	-	-	-	-	-	-
S. Sumatra	1	-	-	-	1	-	-
C. Kalimanten	0	-	-	-	-	-	-
Bali	3	-	-	-	2	-	1
S. Sulawesi	0	-	-	-	-	-	-
Ambon	2	-	-	-	1	1	-

TABLE 79

REGULAR[a] CONSUMPTION OF FORTIFIABLE AGENTS

RANDOM SAMPLE

(STUDY IV)

Age (years)	Total n	Percent Consuming Regularly[a]		
		MSG	Wheat	Sugar
0	1034	13	39	20
1	1102	63	58	56
2	1031	81	58	63
3	1079	80	56	66
4	961	83	58	70
5	1024	81	57	64
Total[b]	6333	67	54	56
$CL_{95\%}$		66-68	53-55	55-57

a. $\geq$1/week.

b. Includes children of unknown age.

TABLE 80

REGULAR[a] CONSUMPTION OF FORTIFIABLE AGENTS

ABNORMALS (X1B)

(STUDY IV)

Age (years)	Total n	Percent Consuming Regularly[a]		
		MSG	Wheat	Sugar
0	1	0	0	0
1	25	52	52	56
2	70	69	54	63
3	94	77	54	56
4	70	70	53	71
5	92	71	47	45
Total[b]	358	70	51	56
$CL_{95\%}$		68-72	48-54	53-59

a. ≥1/week.

b. Includes children of unknown age.

TABLE 81

REGULAR[a] CONSUMPTION OF FORTIFIABLE AGENTS

(HIGH RISK RURAL AREAS)

NORMAL RANDOM SAMPLE[b]

(STUDY IV)

Area	Total n	Percent Consuming Regularly[a]		
		MSG	Wheat	Sugar
Aceh	100	35	17	51
Bengkulu	78	76	46	40
Lombok	435	42	50	47
W. Java	701	65	48	29
C. Java	868	76	45	44
W. Sumatra	89	57	34	25
S. Sumatra	94	60	26	48
C. Kalimantan	55	64	75	67
Bali	245	70	59	59
S. Sulawesi	223	78	62	84
Ambon	194	82	85	89

a. $\geq$1/week.

b. Random sample less applicable abnormals and matched controls.

TABLE 82

FAMILY CONSUMPTION OF FORTIFIABLE AGENTS

(STUDY IV)

Clinical Class	Total n	% Distribution by Frequency		
		MSG	Wheat	Sugar
X1B:	358			
≥1/day		65.9	8.7	67.6
≥1/week		20.1	42.5	22.1
Total		86.0	51.2	89.7
MC:	340			
≥1/day		66.8	12.6	73.8
≥1/week		19.4	40.6	16.8
Total		86.2	53.2	90.6
NRS:	34,576			
≥1/day		69.8	14.2	75.4
≥1/week		17.8	41.7	15.6
Total		87.6	55.9	91.0

TABLE 83

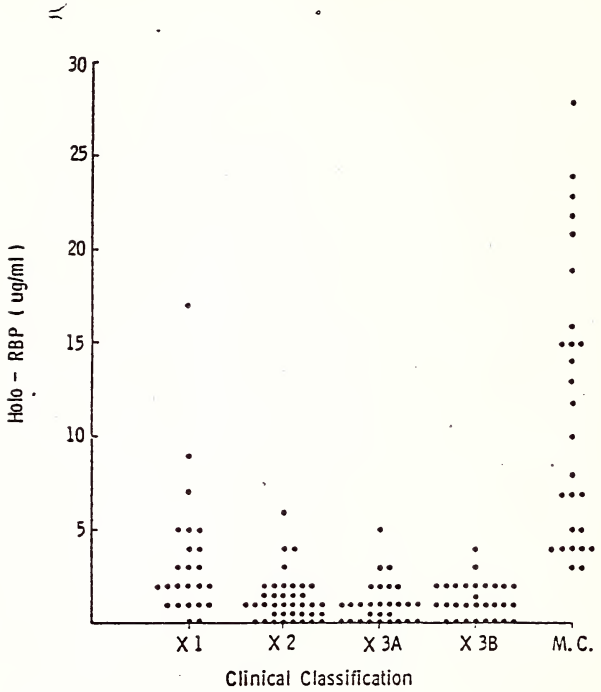
RELAPSE RATE OF CLINICAL XEROPHTHALMIA

(STUDY III)

Followup (months)	Eligible for exam n	Examined n	Examined %	Relapsed n	Relapsed (%)	Relapsed Cum.%
1-2	48	33	68.8	0	(-)	-
3-4	47	20	42.6	0	(-)	-
5-6	44	19	43.2	0	(-)	-
7-10	35	19	54.3	1	(5.3)	5.3
11-14	24	18	75.0	1	(5.6)	10.9

FIGURE 1

INITIAL SERUM HOLO-RBP LEVELS BY CLINICAL STATUS

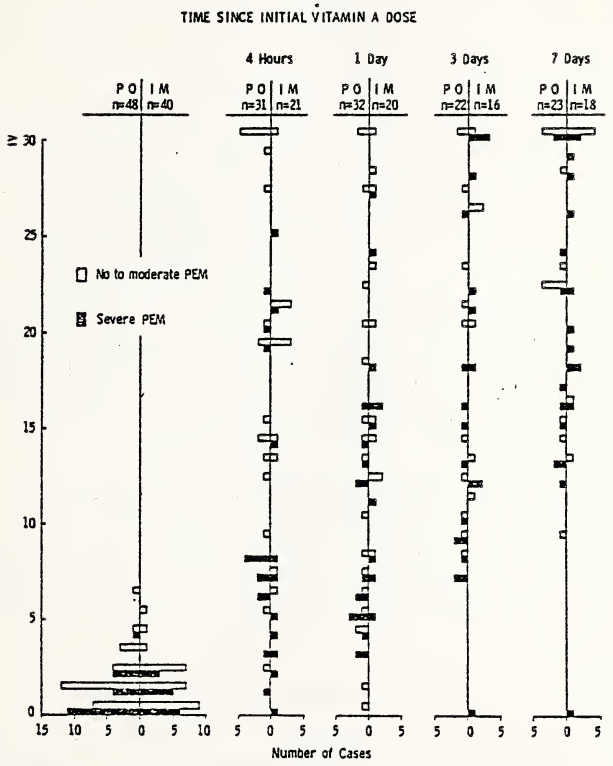


Clinical Classification:

- X1 vitamin A responsive conjunctival xerosis (Study III).
- X2, corneal xerosis, X3A corneal xerosis with ulcers, X3B, keratomalacia, and M.C., matched controls (Study II).

FIGURE 2

HOLO-RBP RESPONSE TO ORAL AND INTRAMUSCULAR VITAMIN A IN CASES OF CORNEAL XEROPHTHALMIA



- Levels at 0, 4, and 24 hours include all cases receiving 200,000 IU orally (PO) or 100,000 IU intramuscularly (IM).
- Levels at 3 and 7 days only include cases that received an additional oral dose, at 24 hours.
- Severe protein deficiency (PEM) defined by an initial serum albumin less than 3.0 gms/dl or transferrin less than 50 mg/dl.

APPENDIX A. BACKGROUND STATEMENT

The high prevalence of xerophthalmia in Indonesia as well as the interest and concern of the Indonesian people and Government made the country an ideal one in which to carry out the comprehensive research project titled "Characterization of vitamin A deficiency and xerophthalmia and the design of effective intervention programs."

For more than a decade, Indonesia has addressed the problem of vitamin A deficiency as a threat to life and health and a major cause of blindness. After extensive research and experimentation with programs, it was declared one of the country's four major nutritional deficiencies. In 1973 the Indonesian Government appropriated funds to carry out a pilot project for distributing high-potency capsules of vitamin A to children between the ages of 12 months and 48 months in selected areas. This project was viewed as a preliminary step in the development of a comprehensive program of distribution throughout the country. WHO provided initial consultation concerning the operational aspects of the project, and UNICEF contributed the vitamin A capsules, vehicles, and other supplies. The American Foundation for Overseas Blind (subsequently renamed Helen Keller International), with partial funding from the United States Agency for International Development, provided resources and technical assistance for design and implementation of a study to evaluate the clinical and operational effectiveness of the pilot project between 1973 and 1975.[1]

General Information about Indonesia

According to the size of its population, Indonesia is the fifth largest country in the world (the estimated population in 1972 was 123 million). The country is composed of 13,500 islands extending for 3,000 miles along the equator, but 95 percent of the population is concentrated on the five major islands: Java/Madura, 65 percent; Sumatra, 18 percent; and Sulawesi, Kalimantan, and Bali, 13 percent. The population density of 1,600

(1,600 per square mile) and annual rate of growth (2.6 percent) are among the highest in the world. Roughly 80 percent of Indonesia's population is rural; more than two-thirds of the remaining 20 percent live in cities with populations of more than 100,000.

Malay is the predominant ethnic group, and 90 percent of the population is Moslem. Sixty percent of the people are literate, and 72 percent of the work force is engaged in agriculture. The staple foods are rice and cassava. Although Indonesia is rich in natural resources, the mean per capita income is only $80 to $100 per month, and several areas are deficient in food. Electricity, sewage disposal, and plumbing facilities are rarely found outside the larger towns.

Infant mortality is high (125 per 1,000 live births) and diarrhea, malnutrition, malaria, and respiratory diseases such as tuberculosis are common. Only one-third of the children who are ill receive medical or paramedical care. There is only one physician for every 20,000 people, and most physicians practice in urban areas.

One of Indonesia's major public health problems is xerophthalmia. Clinical reports of the disease appeared in Medan and Sumatra as early as 1900, and additional reports were received from Bandung and West Java in 1911. Since then, Indonesian scientists have made notable contributions to our understanding of the disease.

Governmental Efforts to Control Vitamin A Deficiency

Control of vitamin A deficiency is primarily the responsibility of the Indonesian Ministry of Health. Since 1975, however, many technical ministries and departments have been working together to combat nutritional deficiencies, not only by medical means, but by non-medical means such as educating the public about nutrition, encouraging home gardening, and fortifying foods with vitamins and minerals.

The various Governmental departments and ministries are members of the Technical Commission for Improvement of the Peoples' Menu, coordinated by the Minister of State for the Peoples' Welfare (Menteri Negara Kesejahteraan Rakyat). Much of the Commission's work is channeled through a Subcommission called Efforts to Improve the Family Nutrition (Usaka Perbaikan Gizi Reluarga, or UPGK). Adoption of national policies and

priorities and appropriation of funds to the Ministries is carried out by the national planning commission (BAPPENAS).

Within the Ministry of Health, control of vitamin A deficiency is handled by the Division of Nutrition and the Academy of Nutrition, both part of the Directorate for Community Health; and the Institute of Health Research and Development and its Institute of Nutrition in Bogor.

HKI's Involvement in the Nutritional Blindness Prevention Project

As a result of the questions raised during the evaluation by the American Foundation for Overseas Blind and the Indonesian Government, the Ministry of Health invited HKI to provide an expert, Dr. Alfred Sommer, to explore the feasibility of and design a plan to accomplish the following: obtain a more precise evaluation of the prevalence of xerophthalmia throughout Indonesia and develop a method of determining the epidemiologic factors and characteristics of individuals and groups at highest risk of nutritional blindness. Working with a Vitamin A Steering Committee composed of representatives of key Government Ministries, such a plan was developed and was accepted by the Government. The following persons agreed to assume leadership roles in these efforts:

- Project Director: Dr. Julie Sulianti Sarosa. Dr. Sarosa was subsequently replaced by Prof. A. A. Loedin, Director of the Institute of Health Research and Development.
- Project Manager: Mr. I. Tarwotjo, Director of the National Academy of Nutrition.
- Clinical Investigator: Prof. T. Sugana, Director of the Cicendo Eye Hospital in Bandung.

Dr. Sommer agreed to remain in Indonesia for three years to provide technical guidance in carrying out the project.

APPENDIX B. PARTICIPANTS IN THE NUTRITIONAL BLINDNESS PREVENTION PROJECT

Major Collaborating Organizations

Ministry of Health, Government of Indonesia

Project Director and Chairman, Vitamin A Steering Committee	Prof. A. A. Loedin, M.D., Ph.D., Sept. 1978-June 1980 Director, National Institute for Health Research and Development, Jakarta
	Prof. J. Sulianti Sarosa, M.D., Ph.D. Sept. 1976-Sept. 1978 Former Director, National Institute for Health Research and Development, Jakarta
Adviser, Vitamin A Steering Committee	R. Soebekti, M.D., MPH Director General, Community Health, Jakarta
Research Manager	Ig. Tarwotjo, M.Sc. Director, Academy of Nutrition, Jakarta
Clinical Investigator	Sugana Tjakrasudjatma, M.D. Director, Cicendo Eye Hospital, Bandung
Statistician	Joko Susanto drs. Center for Nutritional Research and Development, Bogor
Director, Biochemical Studies	Muhilal, Ph.D. Center for Nutritional Research and Development, Bogor
Administrative Officer	Tito Soegiharto, B.Sc. Nutrition Directorate, Ministry of Health, Jakarta

Helen Keller International (HKI), New York

Project Scientist	Alfred Sommer, M.D., M.H.Sc.
Liaison Officer	Carl R. Fritz
HKI Project Manager	Susan T. Pettiss, Ph.D. Director, Blindness Prevention, HKI, New York

Office of Nutrition, Bureau of Technical Assistance, USAID, Washington, D.C.

Dr. Martin Forman, Director

Dr. Irwin Hornstein, Deputy Director

Dr. John I. McKigney, Project Officer

Members of the 1977, 1978, and 1979 consultation teams

USAID Mission, Jakarta

Thomas Niblock, Director

Charles W. Terry, Former Chief, Office of Population and Health

Ken Smith, Former Chief, Office of Health and Nutrition

Imam Satibi, Drs., Sub Directorate, Nutrition Improvement, Section Head, Vitamin A Deficiency

Other Institutions

Biochemical reference laboratory	Prof. John Glover Chairman, Dept. of Biochemistry, University of Liverpool, U.K.
Histopathologic studies	Richard W. Green, M.D. Director, Eye Pathology Laboratory, Wilmer Institute, The Johns Hopkins Hospitals, Baltimore, Md., U.S.A.
	Kenneth R. Kenyon, M.D. Dept of Ophthalmology, Harvard Medical School, Boston, Ma., U.S.A.
Chemotherapeutic agents	Hoffman La Roche Laboratories, Basle, Switzerland
Logistics, equipment, and supplies	World Health Organization United Nations Childrens Fund
Card punching and computer work	Institute of Technology, Bandung El Nusa, Jakarta Institute of Ophthalmology, London University, London, U.K.
Mapping and site selection	Methodology Section, Central Bureau of Statistics, Jakarta
Bacteriologic studies	Bio Farma, Bandung
Parasitologic studies	Department of Parasitology, University of Padjadjaran, Bandung

Pediatric support	Sambas Wiradisuria, M.D. Director of Pediatrics, Hasan Sadikin Hospital, Bandung
Referral and support services	Uton Mochtar Rafei, M.D., MPH, Representative for Health Ministry in West Java, Bandung
	Ghalib, M.D., Community Health Centre, Jatiluhur
	Linda Yusuf, M.D., Community Health Centre, Plered
	Sigit Saroso, M.D., Director, Kubupaten Health Service, Purwakarta
	Rada Hadikusuma and Sukarno, Cikampek Eye Clinic
	Andi Mugni, M.D., West Java Community Health Services, Bandung
	Dra. Sardjono, West Java Nutrition Division, Bandung

Vitamin A Steering Committee

Chairman	Prof. A. A. Loedin, M.D., Ph.D., Sept. 1978-June 1980 Director, National Institute for Health Research and Development, Jakarta
	Prof. J. Sulianti Sarosa, M.D., Ph.D., Sept. 1976-Sept. 1978 Former Director, National Institute for Health Research and Development, Jakarta
Vice Chairman	S. Malasan, M.D., MPH Chief, Nutrition Directorate, Ministry of Health, Jakarta
Adviser	R. Soebekti, M.D., MPH Director General, Community Health, Ministry of Health, Jakarta
Secretary	Ig. Tarwotjo, M.Sc. Director, Nutrition Academy, Ministry of Health, Jakarta

Members	Sugana Tjakrasudjatma, M.D., Director, Cicendo Eye Hospital, Bandung Uton Mochatar Rafei, M.D., MPH, Representative of Health Ministry for West Java, Bandung Darwin Karyadi, M.D., Ph.D., Director, Centre for Nutritional Research and Development, Bogor Misbach, ML, Administrative Staff, National Institute for Health Research and Development, Jakarta Alfred Sommer, M.D., M.H.Sc., Project Scientist, Helen Keller International Carl R. Fritz, Liaison Officer, Helen Keller International

Executive and Publication Committees

Research Manager	Ig. Tarwotjo M.Sc.
Clinical Investigator	Sugana Tjakrasudjatma, M.D.
Administrator	Tito Soegiharto, B.Sc.
Statistician	Joko Susanto, Drs.
Project Scientist	Alfred Sommer, M.D., M.H.Sc.
Liaison Officer	Carl R. Fritz

Study Teams

Study I

Ophthalmologist/Team Leader	G. M. Hussaini, M.D.
Pediatricians	Jusuf Asikin, M.D., March-September 1977 Zein Sulaeman, M.D., Oct. 1977-Jan. 1979
Nutritionist	drs. Suhar Effendi
Supervisory Nurses	Mrs. Tuti Gunawati, B.Sc. Miss Sri Mulyati, B.Sc.
Nurses/Enumerators	Ketut Sumawan Muchlis Rasyid Mamat Rahmat Ade Sopyan

Nurses/Enumerators (cont.)	Tutang Wahyudi Hudori Nurcholis Aleh Ardiyansyah Eddy S.
Drivers	Eman Sulaiman Nuhawi

Studies II and III

Ophthalmologist/Team Leader	Nani Emran, M.D.
Pediatricians	Tien Tamba, M.D. (to July 1978) Emilia Suroto, M.D. (beginning July 1978)
Nutritionists	Mrs. Dedeh Muksin (to Sept. 1977) Muksin, B.Sc. (beginning Oct. 1977)
Supervisory Nurses	Mrs. Apong Amanah, B.Sc. Mrs. Dewi Kania, B.Sc. Mrs. Sriatulanin, B.Sc.
Nurses/Enumerators	Nandang Eman Sudirman Dedy Suherman Mrs. Suyatni Miss Yeti
Hospital Aides	Sutinah Hasminah Ateng Adja Kasmadi Holil

Study IV. Team 1

Ophthalmologist/Team Leader	Edy Djunaedi, M.D.
Nutritionist	Syarifuddin Latinulu, B.Sc.
Nurse	Emod Supriadi
Enumerators	Iman Basuki Maman Darmawan Inda Sudjana Yudi Winarso Heru Utomo
Drivers	Syamsudin Anan Effendi

Study IV. Team 2

Ophthalmologist/Team Leader	Hermawan, M.D.
Nutritionist	Basuki Budiman, B.Sc.
Nurse	Gaos Syarifuddin
Enumerators	E. M. Sukmana Mansursyah Malik Subagyo M. Suseno Witoro Acu Supratman
Drivers	Nanang Mahpudin Aep Saepudin

Study IV. Team 3

Ophthalmologist/Team Leader	Slamet Sedibyo, M.D.
Nutritionist	Djoko Kartono, M.Sc.
Nurse	Adang Mardjuki
Enumerators	Sigit Sedya Leksana Sunaryo Trimo Andi Djohan Chairim Sani Hari Christanto M. Ruslan Effendi
Drivers	Toto Endang

Other Headquarters Staff

Finance Officer	M. A. Soemantri
Supply Officer	R. Isnodi
Senior Secretary	Mrs. Poppy Ersan
Secretaries	Miss Lestari Kadarisman Miss A. Lingsani
Programmer	Agus Hamdani Canny, M.A.
Statistical Secretaries	Mrs. Johanna Hutabarat Miss Retno Gusni
Statistical Assistants	Djadjat Sudradjat Deddy Muhadjar

Statistical Clerks	Farouk Fatah Subagyo Isriyadi M. Sadik Usman Mrs. Nia Prihatin
Administrative Clerk	M. Hellman
Drivers	Opik Sukarna Udi Damyat Agus Sahlin
Aides	Ido Suherman Djudju Djuanda

APPENDIX C. GLOSSARY

Case-control study. See "Retrospective study."

Cornea. The clear central portion of the front of the eye. Xerophthalmic "corneal involvement" includes any changes in the clarity of the cornea due to vitamin A deficiency, from mild haziness to complete destruction with resultant blindness.

Incidence. The rate at which new cases of disease arise over a given period (e.g., one per 1,000 per year) in a population previously free of the disease.

Kabupaten. The major administrative subdivisions (or districts) within a province.

Kecematan. The major administrative subdivisions within a Kubapaten: i.e., a subdistrict that usually contains 5 to 10 villages.

Lebaran. Feast and celebration concluding the Moslem fasting period of Ramadan.

Limbus. The area at the front of the eye where the transparent cornea merges with the opaque sclera.

Longitudinal study. A study in which a defined population is followed over time and the occurrence (incidence) of events is noted.

Posterior pole. The back of the eye, usually the area surrounding the optic disc nasally and the superior and inferior vascular arcades temporally, thus including the macula (the area of sharp vision used in reading).

Prevalence. The rate at which a condition, regardless of its duration, is present in a population.

Prospective study. See "Longitudinal study."

Puskesmas. A local government-run clinic.

Ramadan. Moslem holy month during which the population eats breakfast before sunrise and dinner after sunset and fasts between the two meals.

Retrospective study. A study in which individuals who already have a particular disease (cases) are compared with individuals who do not have the disease (controls) for the presence or absence of potentially associated factors or traits.

RK. Major subdivisions of a village. A village often contains 3 to 10 RK. An RK often contains 3 to 10 neighborhoods or groups of houses (RT).

RT. A neighborhood or group of houses (often 10 to 35), the major subdivisions of a village (RK).

Village. An administrative unit usually contains several hundred households in sparcely settled areas or thousands in densely settled areas. A village is subdivided into RK, which in turn are subdivided into RT.

Warung. A small local store that is reasonably permanent in nature.